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1. Webster, C.W., C.M.A.J. Oct. 1953.

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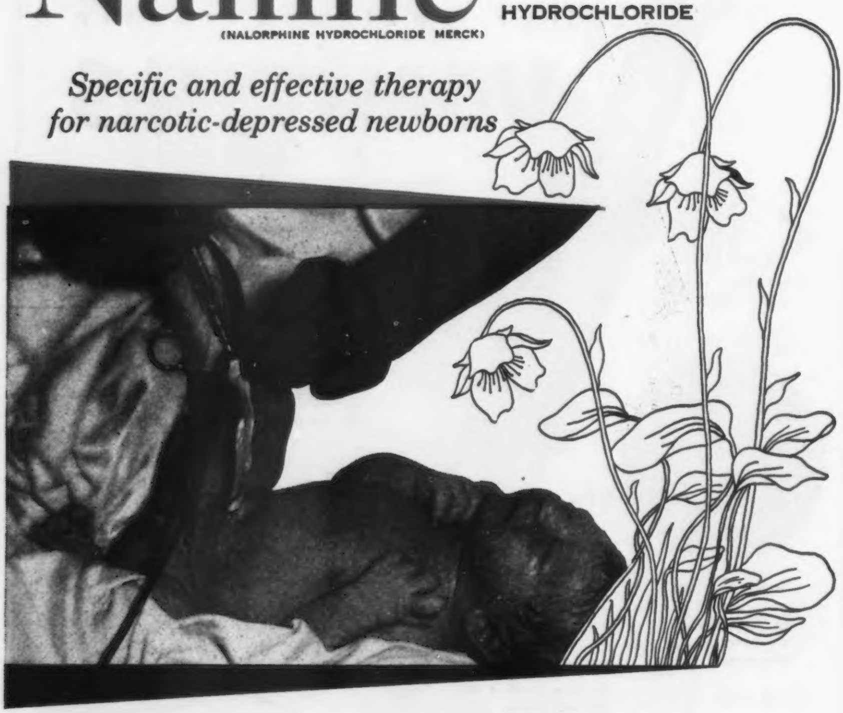

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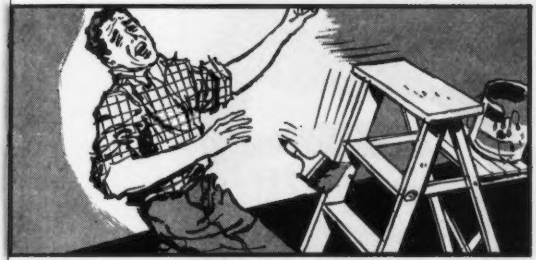

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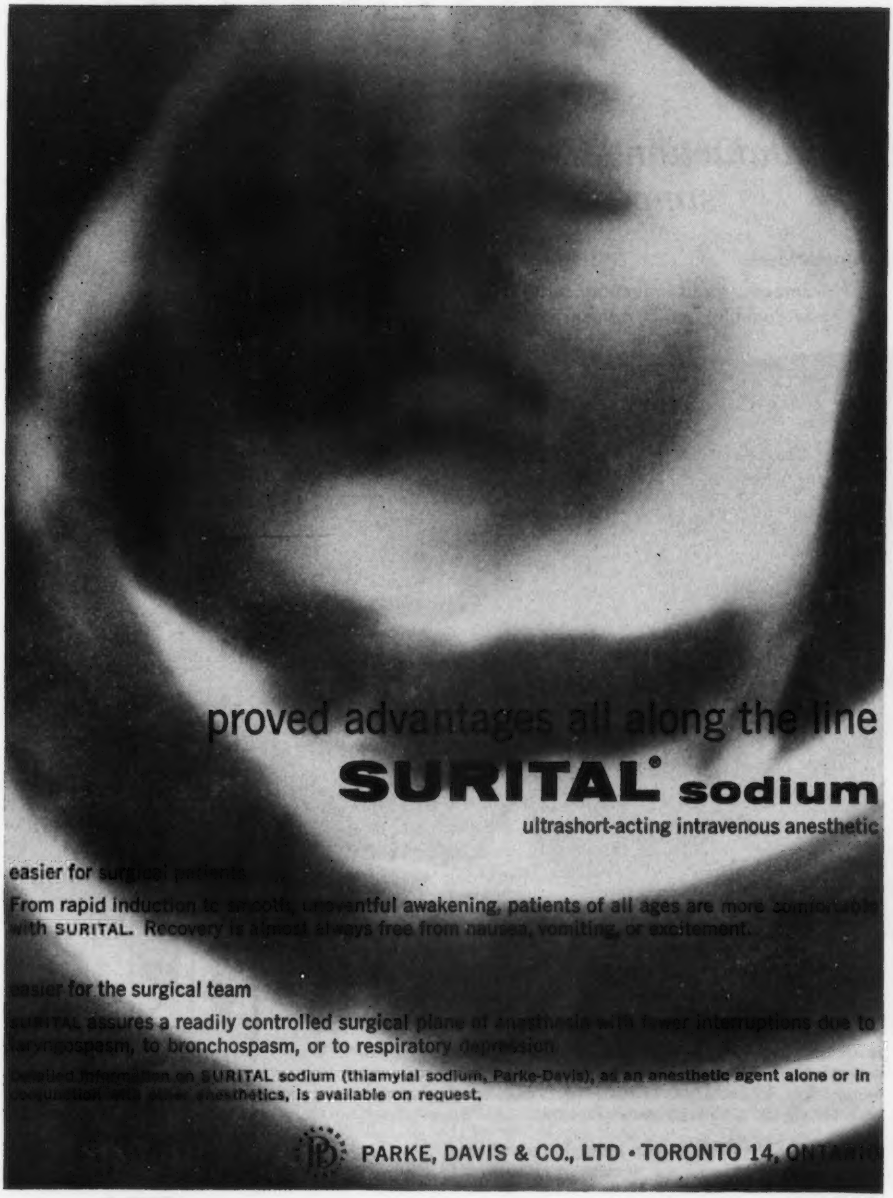

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*Simpson, R., Abrams, B., Gordon A.: Cardiac Monitor for detection and differentiation of cardiac standstill, ventricular fibrillation or peripheral vascular collapse during surgery. S.G.&O., 105:110-113, July, 1957.

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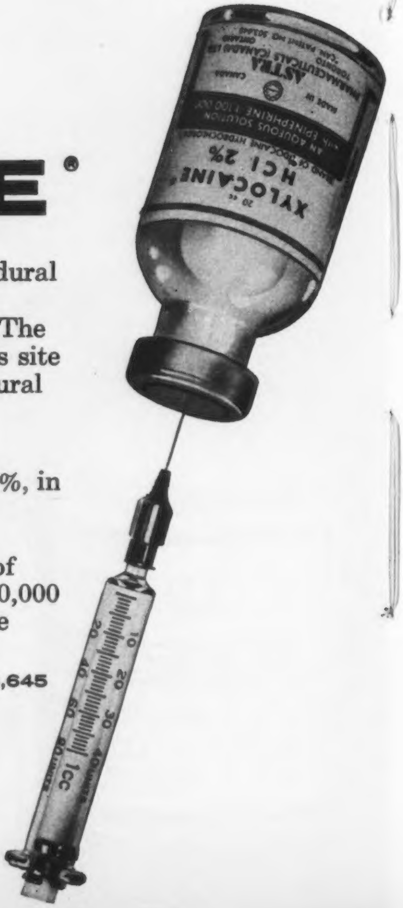

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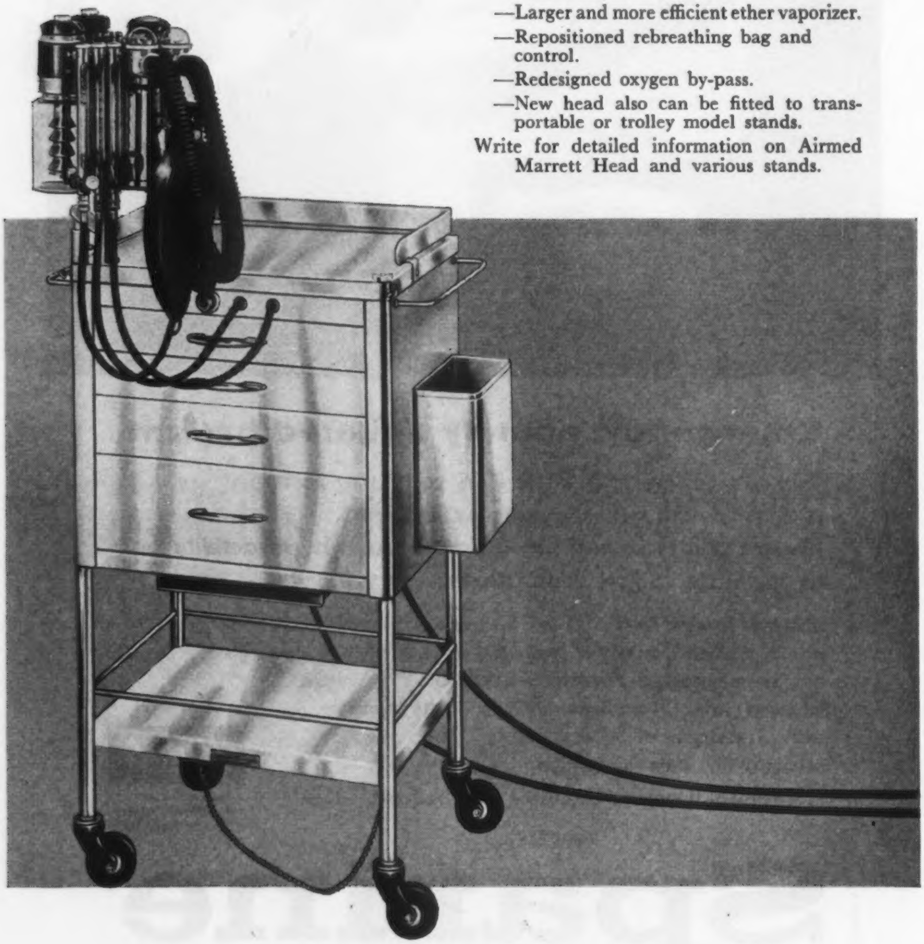

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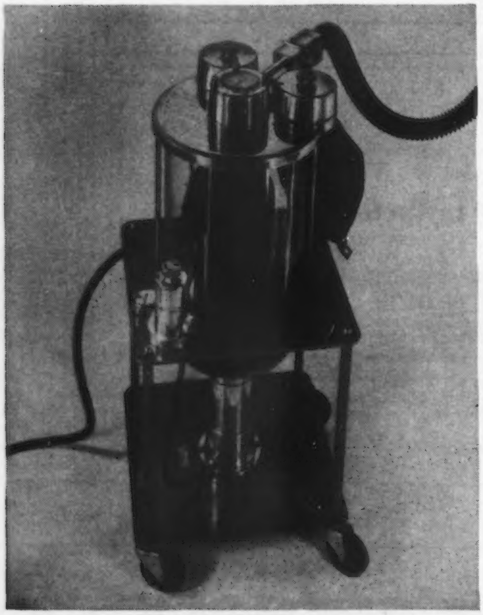

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EDITORIAL

Group Practice of Anaesthesia

We are fortunate in this prosperous young country to have a high degree of professional independence. The well-presented policy of our Society has allowed us to enjoy the privileges of both private and group practice in Canadian hospitals. This satisfactory situation has resulted from sensible negotiations. There have been no emotional convulsions and no exposure of professional problems to the public and to the courts of law. These privileges we must maintain by providing a high standard of professional care at a reasonable cost to the individual patient, and by enlisting and training young physicians with high ideals and ability.

The new trend to group practice in Anaesthesia is a natural solution to the many problems raised by the individual practice of our speciality. More work and greater efficiency are achieved with much less strain on the individual. Even small groups with two or three members will enjoy the results of greater efficiency. Prosperity may be curtailed for a short period, but soon improves with additional scope. With recent large increases in the volume of work, the individual can no longer make the contribution he should. Group membership avoids many of the hazards resulting from overwork and allows an amount of time off duty that is impossible for the individual practitioner. Holidays are no longer associated with loss of income, there is more security against illness, and scientific investigations can proceed without great personal sacrifice. Distribution of public ward responsibilities results in less loss to the individual.

There are also definite advantages to the hospital and a better contribution can be made to all departments.

The department head and his group are more conversant with available people when additions are made to the staff. Co-operative practice facilitates the procurement of people with special ability, and the acquisition of special skills by present members. As a result there is soon a particularly efficient individual for each clinical problem.

Greater individual financial security soon reflects its value. There is more time available for clinical investigation, participation in committee responsibilities and teaching. The twenty-four hour demands of obstetrical and emergency departments can be much better met and the hazards incidental to fatigue avoided by properly prepared duty schedules.

A group provides the necessary people for other essential services, such as recovery room supervision, oxygen therapy, preoperative and postoperative rounds, diagnostic and therapeutic blocks and consultations.

Professional activity can be combined with the maintenance of independence in financial matters, but most groups pool their financial as well as their professional resources.

The co-operative efforts must result in an integrated unit with a good morale. The chief seldom needs to enforce discipline. On the other hand, he must quickly sense individual dissatisfaction and correct it at once. In my opinion, there are two main causes for such unhappiness in an organization of this kind. One is a sense of improper distribution of the duty load. Allowances must be made for administration. Senior members must be responsible and have time available for the business office, the treasurer's books, equipment, the secretarial duties and teaching, but no member can do twice the work of another and be content. Everyone must work and produce; and the seniors must carry the responsibility and provide professional and moral support as well.

The other danger in group practice is that of personal financial dissatisfaction. There may be rumblings of discontent to which the department head may be oblivious. The group should be composed of partners with complete control of their own finances. Statements should be supervised and audited. In other words, simple good business administration is essential. Good business administration can keep people happy. The senior partner will be content and the junior will be happy with his fair treatment, and loyal as a result.

Within the next decade most Canadian anaesthetists will participate in this type of practice. In both private and hospital practice across the country, groups of two or more anaesthetists will provide more efficient co-operative service. We will have problems, but fewer than the anaesthetist of other countries. Progress will only result when we solve our own problems intelligently, by an individual response to each unique situation that arises. We must avoid trying to apply ready-made solutions from the experiences of others, for this will not work. Articles in journals are written by authors with experience only in their own problems. We must, therefore, be prone neither to copy nor to criticize.

Argument will not win for us the approbation of our critics. The newly formed group is often the butt of sly insinuations by others who feel that group practice is the dream child of the astute anaesthetist who, in his zeal for prosperity, thrives on professional and economic exploitation.

There will be justifiable speculation as to our ability to manage our own affairs until group practice has withstood the tests of time. During that period our administrative and surgical colleagues will have to be convinced that the funds of the group are being utilized to provide the optimum number of capable anaesthetists. The loyalty and effectiveness of our own staff members will depend on their personal satisfaction in the effective and honest distribution of personal duties and the resultant income. It will soon be known far and wide whether our staff members leave for reasons of ability to be considered for more senior posts, or for reasons of personal dissatisfaction.

A. B. NOBLE, M.D.

EDITORIAL

LE GROUPE D'ASSOCIÉS EN PRATIQUE DE L'ANESTHÉSIE

DANS CE JEUNE PAYS PROSPÈRE, où nous vivons, nous sommes tout à fait favorisés d'observer l'existence d'une grande indépendance professionnelle. La politique diplomatique de notre société d'anesthésistes nous a amené à pouvoir dans nos hôpitaux canadiens, opter pour la pratique individuelle de la spécialité ou pour le groupe d'associés en pratique. Cette situation agréable est le résultat de longues discussions. Sans bruit et sans heurt, à l'insu du public et en dehors des cours de justice, cette conception de la pratique de la spécialité s'est réalisée. Il nous faut abonder dans ce sens pour pouvoir continuer à donner des soins professionnels de haute qualité sans frais excessifs de la part du malade. Le maintien de cet état de chose dépend également du recrutement et de la formation de jeunes médecins doués d'une grande habileté et d'un idéal aussi grand.

Cette nouvelle tendance à l'association pour pratiquer la spécialité est la résponse toute trouvée à plusieurs problèmes qui se posent dans la pratique individuelle de notre spécialité. Plus de besogne réalisée, plus de rendement et, pourtant, pour l'individu moins de surmenage. Même les associations de deux ou trois spécialiste peuvent observer un meilleur rendement. Momentanément, le chiffre d'affaires peut baisser, mais en peu de temps il s'améliore et d'autres possibilités apparaissent. Quand la somme d'ouvrage devient trop grande, l'individu ne peut plus suffire à la tâche. La pratique en groupe prévient les risques de surmenage et permet à l'individu un repos, une détente qu'il lui serait impossible d'avoir en pratique individuelle.

Ainsi, les vacances ne deviennent plus une privation de revenus; en cas de maladie, la sécurité est accrue; les recherches scientifiques peuvent être entreprises sans trop de sacrifices personnels. En plus, le soin des malades de l'assistance publique devient moins onéreux pour l'individu.

A part cela, l'hôpital retire de cette association de grands avantages à cause de la contribution plus efficace possible avec tous les autres services.

Le directeur du service et son groupe sont plus avenants pour les candidats possibles quand il faut augmenter le nombre des membres du service. Cette association peut permettre l'embauchement, l'adjonction d'un individu possédant des qualités ou des talents spéciaux ou encore permettre a un individu d'acquérir des connaissances et de l'expérience dans une section particulière de la spécialité. Il résultera de cela bientôt qu'il y aura dans le groupe un individu expert pour chaque catégorie de pathologie ou de problèmes cliniques.

Une plus grande sécurité économique aura bientôt son écho. Les temps libres sont plus nombreux pour faire des études cliniques, prendre part aux responsabilités des différents comités et aussi faire l'enseignement. Le service de 24 heures de l'obstétrique et de l'urgence peut s'organiser plus facilement et les risques possibles dûs à la fatique peuvent être évités en organisant adéquatement les cédules opératoires.

Habituellement les associés fournissent le personnel médical spécialisé pour les sections essentielles: la salle de réveil, l'oxygénothérapie, les visites pré- et post-opératoires, les blocages thérapeutiques et de diagnostic et les consultations.

L'activité professionnelle peut être associée en laissant à l'individu son indépendance économique, mais la plupart des associations mettent en commun aussi bien leur travail que le fruit de ce travail.

Les efforts de chacun sont intégrés dans une unité dont le moral est bon. Il arrive rarement que le chef doive recourir à la discipline. Par contre, il doit découvrir précocement les malaises et les corriger aussitôt. A mon avis, il y a deux sources principales de malaises dans une semblable organisation. L'une d'elles est l'impression d'une distribution inégale du travail quotidien. Il faut faire des prévisions pour l'administration. Les membres plus âgés doivent prendre les responsabilités, avoir du temps libre pour la surveillance des affaires, la tenue des livres, l'achat du matériel, le travail du secrétariat et de l'enseignement, mais personne ne peut réaliser longtemps une somme de travail double de celle d'un autre et être satisfait.

Chacun des membres doit travailler à la production, les plus âgés prenant les responsabilités et fournissant le prestige professionnel et le support moral aussi bien que le travail.

L'autre source de mécontentement peut venir de l'aspect économique. Il peut survenir des émanations de mécontentement que le directeur du service peut laisser passer sans y porter attention. Le groupe devrait être composé d'associés dont les revenus demeurent sous le contrôle individuel. Les livres devraient être surveillés et audités. En d'autres termes, il s'impose que l'administration économique soit simple et saine. Une bonne administration peut perpétuer le bonheur. Les ainés seront satisfaits, les juniors seront heureux de leur sort et, en retour, loyaux.

D'ici une dizaine d'années, la plupart des anesthésistes canadiens feront partie de ce genre d'organisation. Aussi bien en pratique privée qu'en pratique hospitalière, les groupes de deux anesthésistes et plus deviendront en mesure de fournir des services plus efficaces dans tout le pays. Nous aurons probablement des problèmes mais, sans doute, moins nombreux que ceux des anesthésistes des autres pays.

Le progrès se fera sentir seulement le jour où nous aurons résolu nos problèmes intelligemment en apportant une solution à chacune des difficultés qui naîtra. Nous devons éviter d'essayer d'appliquer des solutions trouvées par les autres, cela ne peut pas fonctionner. Les articles dans les revues sont écrits par des auteurs expérimentés seulement dans leurs propres problèmes. En conséquence, inutile de copier et de critiquer.

La discussion ne nous gagnera pas l'assentiment de ceux qui critiquent. La formation d'un nouveau groupe d'associés donne souvent lieu à des insinuations tendancieuses de la part des autres. Voilà le sentiment qui en résulte: la pratique de la spécialité en groupe est l'enfant désiré de l'astucieux qui veut profiter de l'exploitation professionnelle et économique dans son désir de prospérité.

Il y aura probablement de la spéculation proportionnelle à notre habileté à gérer nos affaires jusqu'à ce que l'épreuve du temps soit faite. Entre-temps, il nous faudra convaincre administrateurs d'hôpitaux et confrères en chirurgie que les revenus du groupe ne sont utilisés que dans le but de leur fournir la quantité voulue et la plus haute qualité d'anesthésistes. La loyauté et le rendement de nos associés ne tiendra qu'à leur satisfaction en ce qui concerne la distribution honnête des obligations personnelles et de leurs récompenses. La rumeur va se répandre rapidement et à grande distance si tel ou tel associé a quitté le groupe pour occuper un poste plus important ou pour des raisons personnelles de mécontentement.

A. B. NOBLE, M.D.

THE EFFECT OF CHLORPROMAZINE ON HAEMOSTASIS*

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RECENT STUDIES INDICATE that the lethal effect of experimental, traumatic and chronic haemorrhagic shock is decreased or prevented by pre-treatment with chlorpromazine (1,2). In animals this treatment also attenuates the deleterious influence of bacterial invasion, and when bacterial contamination does occur, congestion and haemorrhage in the bowel does not develop (3). In a clinical study of patients undergoing surgical treatment for pulmonary tuberculosis, it was found also that pre-treatment with chlorpromazine possibly prevented or minimized the decompensatory uptake of blood following severe or prolonged haemorrhage and improved the postoperative course of these patients (4).

This protective action of chlorpromazine has been partially explained on physiological, pharmacological and psychological grounds. *Physiologically*, the major known effect of the drug is to decrease peripheral vascular resistance. This causes hypotension and reduces the head of pressure in the peripheral circulation (5, 6). Zweifach and associates believe that the protection afforded by chlorpromazine is due to the block of neurogenic peripheral vascular control and a hyper-reactive response by the arterioles and venules to vaso-active materials in the circulation during stress (7). This hyper-reactivity sustains regional blood flow in the presence of a decreased circulating blood volume more effectively than sympathetic over-compensation in response to stress as seen in the unprotected or unblocked peripheral circulation. This effect is noted both in the visceral and in the peripheral (skin) circulation. The hyper-reactivity of arterioles and venules is considered a favourable sign, indicating that the deleterious pooling of blood in the splanchnic area, as seen in irreversible shock, has been eliminated and that a sustained circulation of the skin and peripheral vascular bed is present in spite of depletion of the blood volume.

Pharmacologically, there is a potent anti-adrenalin effect, a protective action on the heart against epinephrine-induced arrhythmias of chloroform, cyclopropane and trichlorethylene; a slight anti-histaminic effect, an anti-acetylcholine (parasympatholytic) effect; and a potent anti-5-hydroxytryptamine effect. There is also a moderate local anaesthetic effect and a "pharmacological leucotomy" which extends from the level of the cortex to the brain stem and to the cervical ganglia (8, 9, 10, 11, 12, 13).

Psychologically, chlorpromazine suppresses primary epinephrine-precipitable subcortical warning or tension anxiety. It exerts only an indirect influence on the secondary cortical manifestations, consisting of the traumatic state of the ego, in inverse proportion to the degree to which important ego functions have been

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disrupted in the direction of paralysis or inhibition by the anxiety. These are the reasons why chlorpromazine is most effective in manic states or severe anxiety states. These conditions are most directly power-driven in the direction of excitation by epinephrine-precipitable tension anxiety, and in which important ego functions are weakened least. The majority of these neuro-psychological effects are mediated through the reticular activating system (14, 15).

Other sources of chlorpromazine's protective action have been sought. It is possible that it has some effect on haemostasis and on the distribution of circulating blood volume. These two were, therefore, studied in patients who were under the stress of preparation for an elective surgical operation. The following is the report on the effect of chlorpromazine on haemostasis.

In haemostasis three mechanisms must be studied by the clinician: the maintenance of the integrity of vessel walls, the clumping of blood platelets and agglutination of red cells, and the coagulation of the blood. As noted by Jaques (16), if two of these are impaired it is unlikely that haemorrhage can be prevented. Trauma results in contraction of the damaged vessels and decrease in vessel permeability which is partly dependent on liberation of a vasoconstrictor substance, 5-hydroxytryptamine, from platelets. The platelets along with the red cells serve as a mechanical plug at the site of injury, contribute thromboplastin to the third mechanism of defence, the clotting process, and influence clot retraction to produce a firm blood clot. The release of 5-hydroxytryptamine and epinephrine by the platelets causes agglutination of the plug.

The coagulation of the blood consists of a series of rather complicated biochemical reactions. The basic mechanisms of coagulation can be considered as taking place in three phases in a step-wise fashion as suggested by Biggs: activation of thromboplastin; transformation of prothrombin to thrombin; and, finally, the formation of fibrin. Defects in clotting may occur in any one of these phases owing to deficiencies of essential clotting elements. Recent investigations have done much to elucidate factors previously unknown which play an important role in the coagulation process. Many of these recently discovered factors can by considered as accelerators of the over-all transformation to evolve fibrin. On the other hand, one must not forget the possibility of the release and appearance of inhibitors of this process.

The activation of the thromboplastin is brought about by platelets (platelet factors) plus thromboplastinogen (normally in the plasma) to form thromboplastin. Secondly, the conversion of prothrombin to thrombin involves thromboplastin plus prothrombin to form thrombin. Several factors speed up these reactions, including ionized calcium, accelerator globulin (labile factor) and convertin globulin (stable factor). Deficiency of accelerator or convertin factors may delay clotting, while inhibitors in the blood may minimize intravascular clotting. Finally, the formation of fibrin must occur from the thrombin and fibrinogen.

During and following operation, poor haemostasis may develop as the result of two primary defects in the clotting mechanism—deficiency of major clotting elements, and deficiency of essential accelerator factors. A minor defect involves excessive production of inhibitors.

In order to follow properly the sequence of the clotting mechanism, a systematic investigation of all facets of coagulation should be undertaken. Such an analysis was attempted in this study to evaluate the effect of the drug chlorpromazine on haemostasis, utilizing the coagulogram recommended by Bell (17). This is similar to the system of the tests advocated by Seegers and a number of other workers (18, 19, 20, 21). In reviewing the literature, Seegers (18) reported conflicting data as to the effects of anaesthetics and respiratory gases on clotting power of the blood. Epinephrine produced hyper-coagulability, while acetylcholine apparently caused fibrinolysis. Parsloe and associates (20) recently studied the effects of opiate premedication, and of muscle relaxant drugs in combination with thiobarbiturates, for induction of anaesthesia and various systems of maintenance on the clotting of blood, and found a variable response that would indicate no obvious derangement of the clotting mechanism.

It is essential in these studies to realize the limitations of the methods used. Changes in the haemostasis of the patient caused by stress or drugs may be in the coagulant or, as mentioned above, in the anti-coagulant phase and may include changes in the rate of physiological formation or destruction of the major elements of blood clotting. Drugs may also act by entering into direct combination with a coagulant or anti-coagulant or influence the release of either from storage depots. The techniques presently employed for the study of these effects may not reveal minor alterations.

The following procedures were employed to determine the effect of chlorpromazine on blood clotting. Studies were carried out on patients who were scheduled for elective operation. Male patients between the ages of 18 and 76 were selected who were well nourished but not obese, and who had relatively normal heart, lungs, liver, blood counts and circulating blood volume. Tests were carried out the day before operation, 45 minutes after the intravenous injection of chlorpromazine, one hour postoperatively (if blood loss and fluid replacement was minor) and two days postoperatively. None of these patients had received ACTH nor were undergoing surgical procedures involving organs which might cause fibrinogenopenia or a bleeding tendency (21). One patient underwent tonsillectomy under local anaesthesia (H.R.). The remainder had thiopental and nitrous oxide and the relaxant d-tubo curare for their anaesthetic.

TECHNIQUES

Hematocrit (PCV) was determined by filling a Sandford-Magath tube to the 1 ml. mark with 1.1 per cent sodium oxalate solution and adding 5 ml. of venous blood into the oxalate, then the tube was stoppered and inverted two to three times. The stopper was then removed and the tube centrifuged at 2,500 r.p.m. for 30 minutes. The volume of the packed red cells excluding the "buffy coat" was read and muliplied by 20 to determine the hematocrit. Normal value is 47 ± 7 per cent for males.

Haemoglobin was determined with cyanmethaemoglobin standard solutions as provided by the National Research Council on a Coleman Junior Spectrophotometer. Limits of confidence in this laboratory are ± 0.37 grams in the 10 to 18 gram range.

Bleeding time was determined by two methods. One (Duke) was carried out in all cases and is reported; the other was discontinued as this procedure is not routinely used. In the Duke method the lobe of the ear was cleansed with alcohol and a 2 mm. cut (length and depth) was made with a No. 11 Parker knife. Every 5 to 10 seconds the droplet of blood was blotted with filter paper until bleeding stopped. The second method (which was discontinued) is the Ivy technique as described by Stefanini. The sphygmomanometer cuff applied to the arm was inflated to 40 mm. Hg and after cleansing the skin of the forearm with alcohol, a 2 mm. cut (length and depth) was made with a No. 11 Parker knife. Drops of blood were collected on filter paper every 15 to 30 seconds until there was complete cessation of bleeding. Normally bleeding stops within 3 minutes.

Clotting time was measured by a modification of the Lee and White method: 10 ml. of venous blood was drawn for each coagulation determination into a siliconed syringe. Immediately, the first 2 ml. of blood were placed in an oxalated tube as were the last 5 ml. The middle 3 ml. were placed, 1 ml. in each of three, 10 × 75 mm. glass culture tubes and a stop watch started. The first tube was tilted every 30 seconds for the first 3 minutes and then every 15 seconds thereafter until a clot formed. The second tube was then tilted every 15 seconds until a clot appeared and finally the third tube was likewise tilted. The formation of a clot in the third tube was taken as the end point and recorded as the clotting time. Normal values range from 7 to 15 minutes. The oxalated blood was used in the remainder of the study.

Prothrombin determinations. The one-stage method modified from Quick (22), was used. The measurement of the plasma clotting time (prothrombin time) after the addition of thromboplastin and calcium indicates the minimal interval that elapses before a microscopic fibrin clot results from the conversion of prothrombin to thrombin. The value indicates the velocity and amount of thrombin formation from the interaction of prothrombin with calcium, thromboplastin and certain "accessory" substances; the velocity of the thrombin-fibrinogen interaction and deposition of the insoluble fibrin gel; and the competitive effect of antithrombin inactivating the thrombin. The prime purpose of the one-stage prothrombin method is to measure the over-all velocity of thrombin elaboration. However, no indication is given of the mechanism of thromboplastin formation since the latter is added artificially to the system. The one-stage procedure was modified upon occasion for the detection of deficiency of proconvertin (factor VII) (23). For this a small amount of human serum was added to the experimental plasma in the one-stage prothrombin. Fibrinogen levels were measured according to the technique described by Quick (22). Normal is 1.5 to 3.5 mg./ml. plasma.

For the specific determination of prothrombin, the two-stage method described by Ware and Seegers was used (24). This depends on the entire conversion of prothrombin to thrombin, which is then measured by the clotting of a fibrinogen solution previously standardized against known amounts of thrombin. For this

TABLE I

Patient	Time	Age	Height (in.)	Weight (lb.)	B.S.A. (sq.m.)	Blood pressure (mm.Hg)	Pulse rate (/min.)	Hbg. (gm.)	R.B.C. (×10⁶)	PCV (%)	Dose Cpz. (mg.)
CT	*a*	18	67	122	1.63	120/70	84	16.5	5.29	50	25
	b					124/74	112	15.2	4.80	47	
	c					120/80	100	16.2	4.95		
	d					120/70	80	16.2	5.23	51	
HR	*a*	20	73	169	1.97	150/70	80	15.7	5.47	46	25
	b					110/60	120	16.6	5.30	49	
	c					170/90	120	16.0	5.01		
	d					124/60	64	15.7	5.03	52	
JR	*a*	28	68	161	1.85	124/80	80	16.2	4.76	48	24
	b					112/78	80	15.5	4.98	45	
	c					132/78	64	15.0	4.47	48	
	d					130/80	60	16.5	4.87	48	
WC	*a*	33	70	161	1.87	120/80	92	15.5	5.00	45	40
	b					108/80	96	15.7	4.61	45	
	c					120/90	88	16.0	4.72	44	
	d					126/88	72	16.2	5.00	45	
IA	*a*	37	69	210	2.08	130/70	80	14.6	4.61	46	40
	b					110/82	92	14.6	4.68	44	
	c					114/56	72				
	d					124/80	76	14.0	4.80	41	
WS	*a*	43	63	157	1.73	140/85	82	17.4	5.53	51	25
	b					130/86	74	17.2	5.50	50	
	c					140/80	88	15.1	4.48	49	
	d					136/80	76	15.7	4.86	44	
WG	*a*	50	71	174	1.97	140/80	80	16.7	5.21	48	30
	b					130/80	102	16.2	5.09	49	
	c					110/70	78	16.0	5.08		
	d					130/80	80	15.0	5.03	50	
WH	*a*	53	68	130	1.68	110/70	70	14.4	4.83	42	25
	b					90/46	76	14.6	4.65	43	
	c					112/72	78	14.7	4.66	42	
	d					110/66	70	14.4	4.73	37	
JM	*a*	57	69	160	1.86	110/60	80	16.7	5.20	47	25
	b					110/70	60	15.7	5.14	48	
	c					110/60	80	14.8	4.99	50	
	d					128/74	76	14.2	4.75	48	
CD	*a*	66	73	143	1.85	116/72	84	13.3	4.57	41	25
	b					90/62	88	11.9	4.18	50	
	c					110/70	100			42	
	d					120/72	84	14.0	4.40	44	
FK	*a*	67	67	145	1.75	120/74	68	14.4	4.59	40	25
	b					110/69	96	14.0	4.36	45	
	c					114/70	76	14.0	4.71	43	
	d					120/60	70	13.5	4.65	40	
DC	*a*	68	69	142	1.77	140/70	80	11.5	3.53	42	25
	b					130/80	74	11.9	3.96	40	
	c					154/90	64	10.0	3.51	42	
	d					140/60	76	12.5	4.42	42	
GT	*a*	76	72	195	2.08	130/80	74	11.5	3.84	40	25
	b					100/58	86	11.0	3.31	40	
	c					110/60	72	11.1	3.72	32	
	d					130/80	80	11.3	3.70	35	

a—Preoperatively.
b—45 minutes after premedication
c—1 hour postoperatively
d—2 days postoperatively

TABLE II

Patient	Time	Dose Cpz. (mg.)	Capillary resistance	Bleeding time (sec.)	Clotting time (min.)	Clot retraction (ml.)	Platelets (×1000)	Prothrombin consumption (%)	One-stage prothrombin (sec.)	Two-stage prothrombin (%)	One-stage with proconvertin (sec.)	Fibrinogen (mg./ml. plasma)
CT	*a*		0	30	9	.4	258	10	15.0	100		3.0
	b	25	0	30	11.5	.38	286	10	14.6	110		3.6
	c		0	70	13	.38	210	10	17.2	110		6.0
	d		0	40	11.5		205	10	15.0	100	14.6	
HR	*a*		0	90	11	.43	282	10	13.2	60		2.3
	b	25	0	40	12	.43	266	10	16.6	60		1.0
	c		0	55	10		280	10	14.0	100		1.0
	d		0	75	12	.36	275	10	19.7	100	14.8	2.0
JR	*a*		0	35	7		200	10	13.6	60		7.0
	b	25	0	30	8		260	10	14.8	55		2.9
	c		0	30	6	.35	204	10	13.6	70		2.6
	d		0	40	17		270	15	13.8	100		2.9
WC	*a*		0	30	12	.30	181	25	15.6	110		2.0
	b	40	0	30	15	.28	291	20	15.4	90		1.0
	c		0	90	13	.30	181	10	16.0	120		
	d		0	35	17	.10	235	17	17.0	80	15.0	
IA	*a*		0	75		.43	372	10	12.7	67		1.3
	b	40	0	60	11	.45	263	10	22.5	40		1.0
	c		0		7	.37	275	10	12.4	40		1.0
	d		0	45	8.5	.45	202	10	11.0	70		1.7
WS	*a*		0	45			167	10	13.2	72		2.0
	b	25	0	35		.35	256	10	16.6	67		1.7
	c		0	30	7	.42	232	10	14.0	72		1.4
	d		0	30	11	.35	242	10	19.7	70		2.3
WG	*a*		0	95	10			10	17.2	70		1.0
	b	30	0	55	9	.40	227	10	19.0			0.7
	c		0	55	8		186	10	16.5	100		0.5
	d		0	35	12	.36	241	10	19.6	110	13.8	
WH	*a*		0	120	8	.40	262	10	15.2	70		3.9
	b	25	0	45	12	.38	265	10	17.0	100		2.4
	c		0	60	13			30	16.4	60		2.4
	d		0	30	10	.30	295	10	16.0	60		
JM	*a*		0	40	13	.35	240	10	15.0			4.4
	b	25	0	30	16	.38		10	13.0	80		1.7
	c		0	30	12		170	10	12.0			1.4
	d		0	30	11	.35	168	15	15.4	75		5.2
CD	*a*		0	30	19	.20		40	19.0			
	b	25	0	45	17	.37	200	15	12.4	100		
	c		0		24	.45	150	25	14.0			
	d		0	30	13	.32	220	10	17.2			
FK	*a*		0	60	12	.50	275	10	16.0	67		
	b	25	0	55	7	.32	226	10	18.8	67		
	c		0	60	7	.50		20	17.0	67		
	d		0	30	11		268	20	15.2	100		2.9
DC	*a*		0	45	7			10	13.8			3.0
	b	25	0	45	17	.38	246	10	14.2	50		3.6
	c		0	45	18	.25	242	10	13.8	100		6.0
	d		0	30	15	.25	260	10	13.4	90		
GT	*a*		0	60	18	.42	320	15	15.8			3.9
	b	25	0	35	10		176	10	16.6	50		6.5
	c		0	45	6			15				1.4
	d		0	60	12		235	40	13.0	45		

a—Preoperatively
b—45 minutes after premedication
c—1 hour postoperatively
d—2 days postoperatively

method to be valid, all factors required for complete thrombin elaboration must be present, and thrombin inactivation by antithrombins is avoided by dilution in the system (normally 80 to 110 per cent).

Prothrombin consumption test. When normal blood is placed in a glass test tube, most of the prothrombin will disappear within 60 minutes after the blood is shed. This is believed to be due to its conversion to thrombin. In a severe deficiency of serum prothrombin conversion accelerator (SPCA) and in bleeding states of haemophiloid nature the residual serum prothrombin is far greater after coagulation is allowed to run its course than under normal circumstances. Accordingly, serum containing less that 25 per cent of the parent plasma prothrombin may be considered strong evidence against any of these coagulation defects.

Clot retraction time was measured by the method of Andreassen as quoted by Tocantins (25) and modified as follows. One ml. of blood was allowed to clot in a siliconed (G.E. drifilm SC 87) vessel in the centre of which was a glass rod. The blood adheres to the rod but not to the siliconed vessel. The latter was inverted at the end of 2 hours and the expressed serum collected and measured in a graduate tube (normally 0.25 to 0.35 ml.).

Platelets were counted directly using the method of Kristenson (26) (normal 200,000 to 300,000).

RESULTS

The cases studied are summarized in Tables I and II. An analysis of the coagulation system revealed that changes had occurred in the clotting mechanism of the individual from the time the control was taken until after chlorpromazine was administered. In most instances the changes took the form of a moderately increased clotting time and a prolonged one-stage prothrombin time. However, four of the eleven cases with complete data showed a shortening of the clotting time, so that the prolongation was not necessarily due to chlorpromazine. This indicates the variableness of response or perhaps it indicates that the stress reaction was not adequately suppressed.

The increase in the one-stage prothrombin time was found to be due to a deficiency of proconvertin (factor VII, SPCA). Alterations in the two-stage prothrombin values verified the change in the one-stage prothrombin time. There also appeared to be a slight fall in the level of fibrinogen. No change was noted in the clot retraction value, platelet count or in the prothrombin consumption.

Variations were also found in the postoperative studies, but showed no consistency among the patients studied and are attributable more probably to the anaesthesia and the operation. The stress of the latter may have an effect on the clotting system since it has been found that various forms of stress can elevate the one-stage prothrombin time (27).

The decrease in peripheral vascular resistance by chlorpromazine is produced by the fall in blood pressure in most patients. This was not accompanied by any change in the capillary resistance as measured by the tourniquet test. The control

POSSIBLE EFFECT OF CHLORPROMAZINE ON VASCULAR, PLATELET, & COAGULATION RESPONSE TO TRAUMATIC & SURGICAL BLEEDING. (after STEFANINI & ALEXANDER)

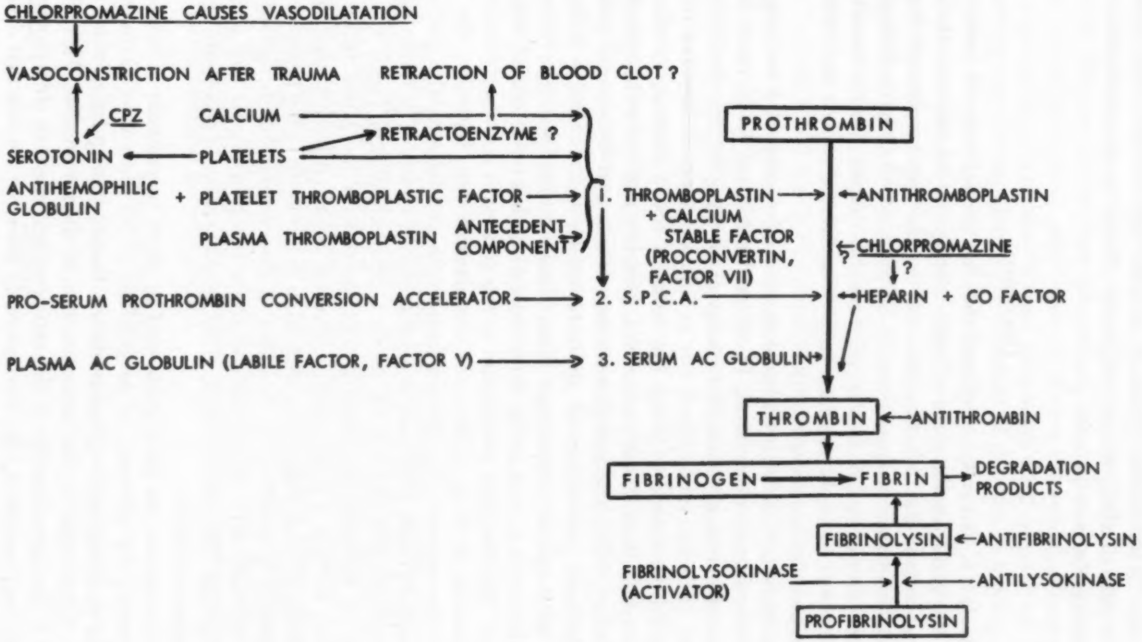
CHLORPROMAZINE CAUSES VASODILATATION
VASOCONSTRICTION AFTER TRAUMA
RETRACTION OF BLOOD CLOT ?
CPZ
CALCIUM
RETRACTOENZYME ?
SEROTONIN
PLATELETS
ANTIHEMOPHILIC GLOBULIN
+ PLATELET THROMBOPLASTIC FACTOR
PLASMA THROMBOPLASTIN ANTECEDENT COMPONENT
PRO-SERUM PROTHROMBIN CONVERSION ACCELERATOR
PLASMA AC GLOBULIN (LABILE FACTOR, FACTOR V)
1. THROMBOPLASTIN
+ CALCIUM
STABLE FACTOR (PROCONVERTIN, FACTOR VII)
2. S.P.C.A.
3. SERUM AC GLOBULIN
PROTHROMBIN
ANTITHROMBOPLASTIN
?
CHLORPROMAZINE
?
HEPARIN + CO FACTOR
THROMBIN
ANTITHROMBIN
FIBRINOGEN
FIBRIN
DEGRADATION PRODUCTS
FIBRINOLYSIN
ANTIFIBRINOLYSIN
FIBRINOLYSOKINASE (ACTIVATOR)
ANTILYSOKINASE
PROFIBRINOLYSIN

FIGURE 1

bleeding time in most patients was quite short and could be attributed to the psychological stress of impending operation. Although chlorpromazine produces an anti-adrenalin and anti-serotonin effect, bleeding time tended to be even shorter than in the control. This may indicate added stress in the immediate preoperative period which is not completely allayed by premedication. This effect persisted into the postoperative period (Fig. 1).

Discussion

Although it is generally recognized that the normal vascular function, particularly of the small vessels, plays an important part in haemostasis, there is far less understanding of this function than of the clotting mechanism itself. This is unfortunate because in approximately 50 per cent of all haemorrhagic disorders no abnormality in coagulation is demonstrable despite present knowledge. Even with the newer concepts one must keep an open mind as new and radical changes in this knowledge are revealed (19).

Before the effect of drugs on haemostasis can be assessed, a working hypothesis of the haemostatic mechanism, based on established facts, must describe the sequence of events in traumatic or surgical bleeding for the clinical investigator. Stefanini (21) has summarized this as follows. Surgical bleeding occurs at the level of the metarteriole. When the vessel is cut, a fleeting, localized vasoconstriction takes place. Shortly afterward, platelets and red cells agglutinate at the site of injury. This physical phenomenon is followed by a more prolonged and more systemic constriction of all metarteriolar vessels, which is attributed to release of 5-hydroxy-tryptamine from disintegrating platelets. Coagulation of blood also seems to start at this time. Once fibrin has been formed, the clot begins to retract. The fibrolytic mechanism in this process is not clearly understood, and the formation of fibrin is the most complicated step. Basically, this mechanism involves the reaction of a platelet factor with anti-haemophilic globulin to form thromboplastin with assistance of several plasma factors. The thromboplastin then reacts with calcium and a stable factor (cothromboplastin, factor VII, convertin) to form an intermediate complex that reacts with the labile factor (factor V, accelerin) to form a prothrombin-convertin agent (plasma thromboplastin, prothrombinase) which converts prothrombin to thrombin in the presence of calcium. As fibrinogen is acted on by thrombin in the presence of an optimal concentration of calcium and a poorly defined factor found in plasma and serum, fibrin is finally formed. The factors supplied by platelets seem to accelerate the formation of thrombin and fibrin.

Chlorpromazine has been postulated to affect haemostasis in two major ways: by increasing the efficiency of coagulation; or by preventing fibrinolysis. On the other hand, Courvoisier (8) has shown that the coagulation time of blood in animals is prolonged by the administration of chlorpromazine. This effect may be related to the anti-adrenalin or the anti-serotonin effect of chlorpromazine.

Kovács and associates (28) have recently shown in animals that chlorpromazine clears lipaemia presumably by mobilizing endogenous heparin. Their hypothesis is supported by the fact that the clearing effect appears rapidly, bringing about a shift in the lipo-protein pattern similar to that produced by heparin, and that the effect is inhibited by protamine. If a rise in heparin occurs in this way, the clotting mechanism may be disturbed at several points since heparin prevents the activation of prothrombin to thrombin by an anti-prothrombin action, and a powerful anti-thrombin effect inhibits the action of thrombin in converting fibrinogen to fibrin. Heparin also reduces or prevents the lysis and agglutination of platelets and, therefore, reduces production of plasma thromboplastinogen.

Perlick (29) reported that the phenothiazine derivatives used to produce prolonged sleep therapy may increase the heparin content of the blood. Kovács also points out that since the phenothiazine derivatives have come into wide use in therapy, several observations have suggested that thrombo-embolic complications frequently occur following prolonged use of these drugs. On the basis of experiments it might be assumed that owing to the increased release of heparin during prolonged phenothiazine treatment the heparin stores throughout the body become diminished and the interruption of continuous administration may be followed by a sudden decrease of the heparin blood level. The possibility that such a mechanism is in operation was suggested to explain an increased coagulability of the blood *after* the administration of chlorpromazine. However, the evidence regarding human heparin is still very scanty and it would be premature to relate to humans any data obtained from animals.

In this study, the single intravenous injection of a therapeutic dose of chlorpromazine showed no consistent change in platelet count or the clotting time either after the drug or after anaesthetic and the operation. The only significant change was a prolongation of the one-stage prothrombin time (in nine of thirteen patients). This probably indicates an inadequate suppression of the stress response by chlorpromazine in the doses administered.

SUMMARY

A study of the effect of chlorpromazine on the haemostatic mechanism was carried out on thirteen adult male patients in relatively good general health and who were under the stress of preparation for an operation. A reduction in blood pressure indicated a significant decrease in peripheral vascular control, and a decrease in the prothrombin time occurred in most of the patients. These changes did not persist into the postoperative period. Under these clinical conditions and by this technique of study, it was found that chlorpromazine may decrease the coagulability during operation and may increase coagulability postoperatively. The cause of these changes was not revealed.

ACKNOWLEDGMENT

The authors sincerely appreciate the advice and assistance by Professor L. B. Jaques.

RÉSUMÉ

Nous avons fait une étude de l'effet de la chlorpormazine sur le mécanisme homeostatique de treize hommes en bonne santé relative mais subissant le stress

de la préparation à une opération. Nous avons observé une diminution notable du controle vasculaire páriphérique manifesté par l'abaissement de la pression artérielle et une diminution du temps de prothrombine chez la plupart des malades. Après l'opération, ces modifications n'existaient plus. Dans ces conditions cliniques et avec cette façon d'étudier, nous avons observé que le chlorpromazine peut diminuer la coagubilité pendant l'opération et l'augmenter dans les suites opératoires. On n'a découvert l'étiologie de ces modifications.

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PROMETHAZINE AND THE CIRCULATORY RESPONSE TO TILTING[*]

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PROMETHAZINE HYDROCHLORIDE (Phenergan), introduced into anaesthetic practice by Laborit (1) and employed as an integral part of the "lytic cocktail" (2), was shown by experiment on animals to possess many of the properties characteristic of the amine derivatives of phenothiazine:

Actions of Promethazine

Anti-histaminic
Anti-emetic
Sedative and hypnotic
Potentiation of anaesthetics, analgesics, hypnotics, muscle relaxants
Local anaesthetic
Quinidine-like, on cardiac muscle
Antagonistic to adrenaline and acetylcholine
Protective, against shock
Anti-convulsant
Spasmolytic
Hypothermic

In man, however, the pharmacological actions of promethazine have been frequently obscured by simultaneous administration of other phenothiazine derivatives. Studies dealing with the use of promethazine in clinical anaesthesia (5, 6), and in obstetrics (7), and with its circulatory effects in a small number of patients undergoing cardio-angiography (8), have been complicated by prior administration of analgesics or barbiturates.

While it appears from clinical evidence that the central depressant and potentiating actions of promethazine are the ones most sought after and utilized by the anaesthetist, further investigation is required to clarify and define this use. The suggestion that the drug is valuable as a sedative and anti-emetic drug during spinal analgesia (5) indicates that further studies should also be undertaken on the circulatory actions of intravenous promethazine in order to establish whether it shares, in part, the postural hypotensive properties so characteristic of chlorpromazine (9).

In this investigation an attempt has been made to assess the action of intravenous promethazine on blood pressure, by continuous intra-arterial recording, and to observe the response to the circulatory stress of maintaining a 60-degree head-up tilt for fifteen minutes before and after administration of the drug. Some inferences have also been drawn in regard to the use of intravenous promethazine in clinical anaesthesia.

METHOD

Eighteen studies were carried out on seventeen unpremedicated male subjects between the ages of 17 and 60 years, who had undergone or were awaiting a wide variety of surgical procedures. The only criteria involved in selection of individual subjects were their ability to lie comfortably in the supine position, and their availability.

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At the start of each study a slow intravenous saline infusion was established in a forearm vein. A fine plastic catheter was then inserted through a No. 20 needle into the brachial artery at the elbow (of the other arm) and a continuous record of arterial pressure obtained by means of a Lilly capacitance manometer (10, 11) with a Sanborn single channel recorder. Very frequent checks of zero point and of the calibration of the manometer were carried out.

After control records had been obtained with the subject resting in the horizontal position, the table was tilted (not abruptly) into a 60-degree head-up tilt. This position was maintained for fifteen minutes (unless fainting occurred earlier), the subject then being returned to the horizontal. After a few minutes resting, promethazine hydrochloride 50–100 mg. was injected intravenously through the infusion tubing over a period of up to five minutes, as unobtrusively as possible. Fifteen minutes after completing the injection the table was again tilted to the 60-degree head-up position which was maintained for a further fifteen minutes unless fainting necessitated an earlier return to the horizontal.

RESULTS

The subjective effects of intravenous promethazine appeared pleasant. A feeling of warmth and well-being rapidly developed and for about the first ten minutes after injection a state of sleepy relaxation was characteristic. Slurred speech was always an early feature. The skin appeared warm and dry.

Although all the subjects were drowsy, sleep did not occur, and before long fidgety body movements would accompany a state of obvious mental disorientation. There was some irritability and confusion, with an apparent inability to co-operate or keep still on command. One subject stated subsequently, "I

TABLE I

CIRCULATORY EFFECTS OF INTRAVENOUS PROMETHAZINE

			Arterial blood pressure and heart rate					
Subject	Age (years)	Dose (mg.)	Control		4–5 min. after start of injection		14–15 min. after completing injection	
J.G.	37	50	155/86	86	163/91	82	168/100	78
M.C.	35	50	114/88	66	131/101	68	132/103	72
J.McC.	36	50	130/85	66	129/89	62	133/98	93
G.L.	23	50	108/79	72	108/80	75	122/97	100
K.H.	23	100	119/80	72	119/82	69	123/90	87
J.McL.	23	50	127/80	63	142/94	63	171/109	81
N.G.	17	50	146/85	99	142/91	96	133/80	84
C.H.	18	50	110/52	56	109/57	60	119/66	60
J.McL.	23	50	119/78	64	120/79	69	135/96	114
A.T.	54	50	100/50	60	130/70	60	121/60	66
N.B.	60	50	182/110	84	191/113	72	180/110	76
P.L.	59	50	149/86	58	149/92	64	125/73	62
H.J.	48	50	141/93	72	150/91	69	146/93	88
		50	142/90	90	146/93	88	158/105	72
T.G.	42	100	124/77	72	146/90	78	154/106	112
J.L.	43	50	143/87	69	148/99	78	144/98	75
A.C.	47	50	127/84	78	124/84	96	138/92	98
L.M.	40	50	193/101	76	197/119	76	1821101	76
A.A.	33	100	142/93	81	141/100	72	139/101	99

understood what you meant but could not do it"; another remarked, "I understood what was said, I knew the necessary reply, but could not say it." Disorientation was accompanied by moderate or severe restlessness in fifteen subjects (83.3 per cent); in all three subjects who received 100 mg. of promethazine restlessness was particularly troublesome, and necessitated termination of the head-up tilt after promethazine injection.

Apart from the transient faintness associated with severe hypotension during tilting, malaise and nausea were not encountered.

Blood pressure and heart rate 4–5 minutes and 14–15 minutes after injection of 50–100 mg. of promethazine hydrochloride are shown in Table I. Heart rate was little changed by 4–5 minutes, but had increased by an average of 12.6 beats at 14–15 minutes; this increase is significant ($P < 0.05$). When promethazine 50 mg. is rapidly injected intravenously, immediate tachycardia and transient hypotension may result (Fig. 1).

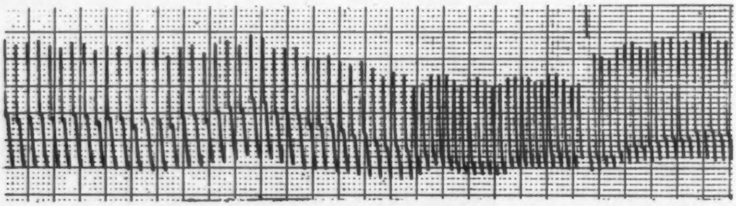

FIGURE 1. Tachycardia and transient hypotension following intravenous injection of promethazine 50 mg.

Increases in systolic and diastolic pressure frequently followed the intravenous injection of promethazine. When restlessness occurred there was usually an obvious association between movement and transient blood pressure increases. The data pertaining to blood pressure and heart rate during tilting is shown in Tables II, III, and IV. Eight subjects maintained the 60-degree head-up position

TABLE II

SUBJECTS TOLERATING BOTH TILTS

		Arterial blood pressure and heart rate					
Subject	Tilt	Before		Within 1st minute		After 15 minutes	
P.L.	Control	160/89	62	148/88	68	144/82	78
	Promethazine	125/73	62	125/65	82	133/60	72
H.J.	Control	159/95	80	155/95	72	140/95	87
	Promethazine	168/110	76	162/116	93	155/105	86
J.L.	Control	147/95	69	141/97	76	136/93	82
	Promethazine	144/98	75	147/99	78	143/104	78
L.M.	Control	196/118	80	189/128	78	186/109	93
	Promethazine	182/101	76	164/100	78	154/94	96
J.G.	Control	163/87	86	160/90	102	146/92	108
	Promethazine	147/88	75	156/94	102	153/95	93
J.McC.	Control	116/78	70	118/86	84	136/100	80
	Promethazine	133/98	93	134/110	104	137/115	102
J.McL.	Control	122/77	70	114/71	75	109/78	96
	Promethazine	171/109	81	154/110	92	147/102	82
J.McL.	Control	113/70	76	114/80	88	117/93	111
	Promethazine	135/96	114	133/100	114	127/95	98

for fifteen minutes without circulatory stress, before and after intravenous injection of promethazine (Table II).

By the end of fifteen minutes two subjects showed marked hypotension, during the control tilt only; after promethazine both withstood tilting without adverse effects (Table III). Four other subjects showed signs of an impending faint during both tilts and were returned to the horizontal. The average time of onset of hypotension in this group was 7.3 minutes during the control tilt and 7.8 minutes during the promethazine tilt (Table III).

TABLE III

SUBJECTS SHOWING HYPOTENSION DURING CONTROL TILT ONLY, AND DURING BOTH TILTS

		Arterial blood pressure and heart rate							
Subject	Tilt	Before		Within 1st minute		Termination		Duration of tilt (minutes)	Terminal effect
C.H.	Control	155/58	68	108/60	70	42/22	84	15	Hypotension
	Promethazine	119/66	60	110/70	78	107/66	82	15	—
A.T.	Control	113/66	66	98/63	70	88/52	82	15	Hypotension
	Promethazine	121/60	66	96/57	82	115/68	82	15	—
G.L.	Control	102/77	72	114/96	102	55/48	108	4	Hypotension
	Promethazine	130/101	90	129/109	123	63/53	90	10	Hypotension
N.G.	Control	128/77	116	115/68	114	49/28	105	7	Hypotension
	Promethazine	133/80	84	131/86	96	60/40	78	6	Hypotension
A.C.	Control	127/84	87	127/89	90	84/55	72	11	Hypotension
	Promethazine	138/92	98	131/95	104	77/51	87	6	Hypotension
M.C.	Control	124/92	78	117/95	81	49/37	48	7	Hypotension
	Promethazine	132/103	72	102/106	93	65/49	66	9	Hypotension

Only one subject developed marked hypotension during the promethazine tilt alone, at 9 minutes (Table IV). Part of this record is illustrated in Figure 2. Three of our other subjects were so restless and generally uncontrollable during the tilt following injection of 100 mg. promethazine that termination of the study was clearly necessitated (Table IV). Wide swings of blood pressure, probably induced by irregular respiratory patterns, frequently accompanied restlessness especially when the subjects were in the head-up position (Fig. 3).

TABLE IV

SUBJECTS SHOWING HYPOTENSION OR RESTLESSNESS DURING PROMETHAZINE TILT ONLY

		Arterial blood pressure and heart rate							
Subject	Tilt	Before		Within 1st minute		Termination		Duration of tilt (minutes)	Terminal effect
N.B.	Control	176/106	78	151/99	80	162/113	96	15	—
	Promethazine	180/110	76	143/100	90	80/62	70	9	Hypotension
K.H.	Control	110/77	63	115/84	92	116/93	93	15	—
	Promethazine	123/90	87	135/110	94	142/103	112	9	Restlessness
A.A.	Control	114/78	72	106/78	76	141/98	84	15	—
	Promethazine	139/101	99	130/94	105	113/64	120	2	Restlessness
T.G.	Control	125/86	80	125/83	92	120/83	92	15	—
	Promethazine	146/105	110	128/91	114	115/78	116	9	Restlessness

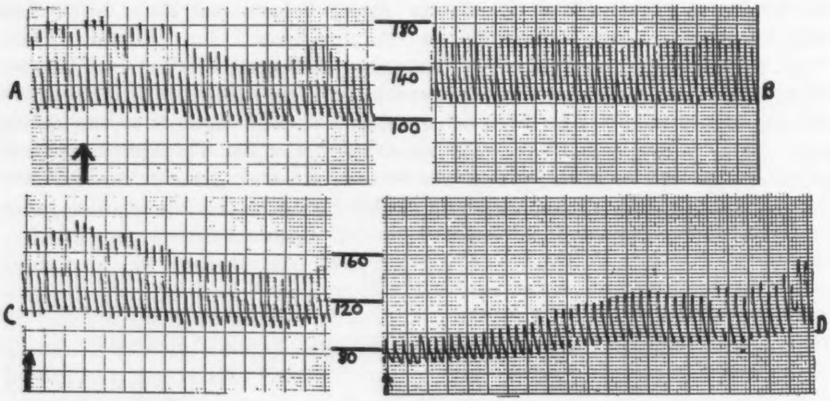

FIGURE 2. Record obtained from one subject showing hypotension during tilt following promethazine injection: A, control tilt; B, after 15 min. in 60-degree head-up position; C, tilt 20 min. after promethazine 50 mg. intravenously; D, severe hypotension after 9 min. in head-up position.

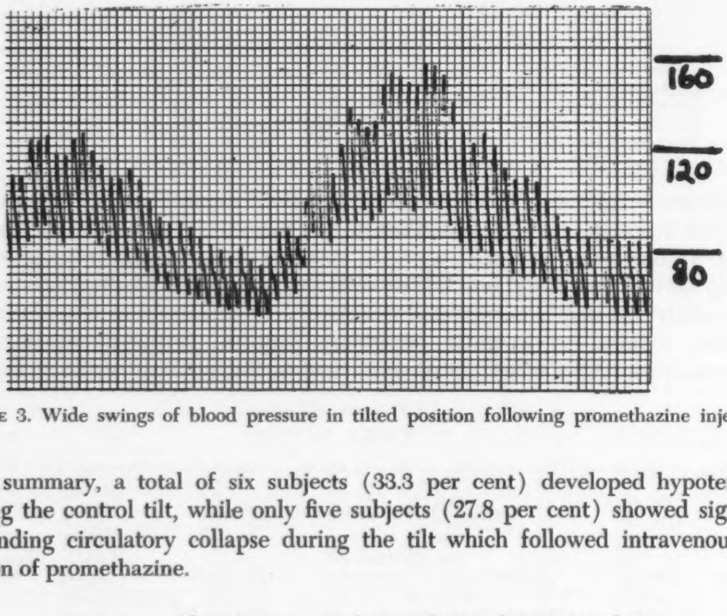

FIGURE 3. Wide swings of blood pressure in tilted position following promethazine injection.

In summary, a total of six subjects (33.3 per cent) developed hypotension during the control tilt, while only five subjects (27.8 per cent) showed signs of impending circulatory collapse during the tilt which followed intravenous injection of promethazine.

Occurrence of hypotension or restlessness during tilting in 18 subjects

Tolerating both tilts for 15 minutes without hypotension	8
Hypotension during control tilt only	2
Hypotension during both tilts	4
Hypotension during promethazine tilt only	1
Severe restlessness requiring termination of promethazine tilt	3

In an attempt to induce further circulatory stress in several subjects while in the 60-degree head-up tilt, they were asked to inspire deeply and hold their breath while tightening their abdominal muscles—a modified Valsalva manœuvre. An example is illustrated in Figure 4. The secondary increase in blood pressure followed by the "overshoot" when airway pressure is released are both present in all four tracings, although in the tilted position, both before (B) and after (E) promethazine injection, the secondary increase in arterial pressure is not maintained as a plateau; this may result from the more prolonged period of breath-holding which reaches 30 seconds in the promethazine tilt (E). With the exception of an increased heart rate, the circulatory pattern following promethazine compares very favourably with that observed before drug administration. In no study was it possible to induce circulatory changes outlasting the well-recognized effects of the Valsalva manœuvre.

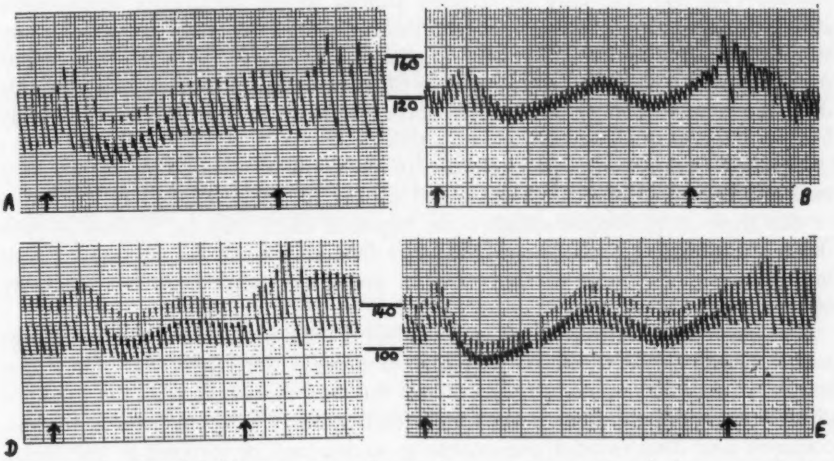

FIGURE 4. Breath-holding in one subject: A, in supine position before promethazine injection; B, during control tilt; D, in supine position after 50 mg. promethazine intravenously; E, during tilt 20 min. after promethazine injection.

DISCUSSION

The circulatory response to head-up tilting may be conveniently utilized in an assessment of premedicant drugs in man. Studies similar to the one employed here have been carried out with morphine (12), Demerol (13) and other synthetic analgesics (14). An increased incidence of hypotension in the head-up position may be expected after injection of these agents.

It appears from this study that promethazine does not depress circulatory compensation to tilting to any marked extent. The tendency revealed by intravenous injection of 50–100 mg. is rather in the direction of an hypertensive response although it seems very likely that this is largely attributable to the marked restlessness which occurred in the majority of subjects studied. The possibility exists, however, that promethazine, when administered in the "lytic cocktail," does not potentiate the postural hypotensive action of chlorpromazine and may even antagonize it to some extent.

The circulatory responses to the Valsalva manœuvre have been extensively studied (see 15) and may be broadly similar to the circulatory mechanisms acting during head-up tilting (16). Failure to cause circulatory collapse in any subject by induction of a modified Valsalva manœuvre following intravenous promethazine, whether in the supine or tilted position, further implies that this drug has a minimum of adverse circulatory effects, at least in the reasonably healthy subjects studied in this investigation.

Intravenous injection of promethazine in doses greater than 50 mg. is probably rarely indicated in clinical practice and cannot be recommended on the basis of this study. A prolonged sedative and hypnotic effect may be obtainable with doses of 50–100 mg. intravenously, but the drug appears to induce marked restlessness when any form of discomfort is present or when enforced inactivity is required.

The impression derived from observations is that promethazine may change a co-operative subject, who is prepared to tolerate some relatively minor discomforts (e.g., the degree of immobility of the arms necessitated by the presence of an intravenous infusion or an intra-arterial catheter), to one who is restless, confused and disorientated and unable to understand or respond to command.

For these reasons it is recommended that promethazine, at least when administered intravenously, should be given only in conjunction with an analgesic drug. The usefulness of small intravenous doses of promethazine has not been assessed from this study, but owing to variations in individual patients it would appear safer to adhere to the principle of simultaneous administration of an analgesic agent even when small doses of promethazine are injected intravenously.

SUMMARY

Continuous intra-arterial blood pressure recording during eighteen studies has shown that promethazine, when injected intravenously in doses of 50–100 mg., does not induce circulatory depression, although tachycardia may occur especially with rapid injection. A tendency for blood pressure to increase appears to be at least partly attributable to the moderate or severe restlessness which frequently occurs.

Induction of a 60-degree head-up tilt before and after intravenous injection of promethazine revealed a somewhat lower incidence of severe hypotension after injection than before. It appears that intravenous promethazine has little depressant action on the circulatory response to head-up tilting and does not share the postural hypotensive properties of chlorpromazine.

It is concluded that, if restlessness is to be avoided, intravenous promethazine should be administered to conscious patients only in conjunction with an analgesic drug. Severe and uncontrollable restlessness may occur following intravenous injection of 50–100 mg. in patients who are required to remain immobile or who are experiencing even minor degrees of discomfort.

RÉSUMÉ

Nous pouvons affirmer, après avoir étudié l'enregistrement continuel de la pression artérielle chez 18 malades, que la prométhazine, injectée dans les veines à la dose de 50 à 100 mgm., ne produit pas de dépression circulatoire bien qu'une tachycardie soit observée occasionnellement surtout quand l'injection a été rapide. Le fait que la pression sanguine a une tendance à monter semble être attribuable en partie du moins à l'état d'agitation plus au moins prononcé que nous observons fréquemment.

La position de Fowler de 60 degrés avant et après l'injection de prométhazine nous a permis de constater une plus faible incidence d'hypotension grave après l'injection qu'avant l'injection. Il semble que l'injection intraveineuse de prométhazine a peu d'effet dépresseur sur la réponse circulatoire à la position de Fowler et qu'elle ne partage pas les propriétés de la chlorpromazine sur l'hypotension posturale.

Nous en venons à la conclusion que, si nous voulons éviter l'agitation, il est préférable d'injecter la prométhazine aux malades conscients seulement et associer une médication analgésique. A la suite d'injections intraveineuses de 50 à 100 mgm. de prométhazine il arrive d'observer une agitation considérable et ingouvernable chez des malades dont on exige l'immobilité ou qui ne ressentent que de légers malaises.

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SOME EFFECTS OF LEVALLORPHAN ON RESPONSES TO MEPERIDINE

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THE PURPOSE OF THIS STUDY was to measure some of the effects of levallorphan on analgesia and respiratory depression produced by meperidine. Of particular interest was the determination of the ratio of meperidine to levallorphan which, when, they are given simultaneously, would provide adequate analgesia without respiratory depression.

METHODS AND MATERIAL

Patients with chronic pain of sufficient severity to require the use of narcotic analgesics served as the subjects for the experiments. They were not told what drug they were receiving or what was expected of them. All subjects were given saline, meperidine, and two ratios of meperidine and levallorphan in successive trials; thus each patient served as his own control and as a basis for comparison. Effects on respiration were measured by testing the response of minute volume to the inhalation of 5 per cent carbon dioxide in oxygen. We believe this to be a more sensitive means of judging the reactivity of the respiratory centre than the measuring of respiratory minute volume while the subjects are breathing room air. Respiration was measured on a 13-litre Collins respirometer just before the injection of the drug, and 15, 30, 60, and 90 minutes thereafter whenever this was practicable. The amount of analgesia was evaluated and recorded with the aid of a scale in which 0 indicated no pain; 1, slight pain; 2, moderate pain; and 3, severe pain. Each patient was questioned regarding the character and degree of pain before and 15 and 30 minutes after the injection and at 30-minute intervals thereafter for a total of 4 hours. Accordingly, differences between the pre-injection pain level and the respective levels following the injection of the drug gave numbers which were used to indicate the amount of pain relief or "analgesia" for each time interval. Thus a difference of 0 meant no pain relief; 1, slight relief; 2, moderate relief, etc. These numbers were added for the entire period of the experiment to yield a numerical expression of total pain relief. Observations of side reactions were also recorded. The patients were supine throughout the time of observation. A period of at least 24 hours separated each experiment. All patients were in pain (Grade 2 or 3) at the beginning of each trial. They were not permitted to receive a narcotic within 6 hours prior to any observation period.

The solution of meperidine (Demerol) hydrochloride contained 50 mg./ml. and that of levallorphan (Lorfan)[1] tartrate 1 mg./ml. Half of the patients received injections by the intramuscular route, and the other half by the subcutaneous route. The standard dose of meperidine was 100 mg. for four of the

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patients and 50 mg. for the other two. The latter were in such poor physical condition that doses higher than 50 mg. meperidine were contraindicated. When levallorphan was administered with meperidine, the two drugs were mixed in the same syringe immediately before injection. The ratios by weight of meperidine hydrochloride to levallorphan tartrate that were studied were 100:1, 100:1.5 and 50:1. All subjects were given meperidine alone and the 100:1.5 mixtures; in addition, three received the 50:1 combination and another three the 100:1 mixture.

RESULTS

The effects of meperidine alone and of the meperidine-levallorphan mixtures on the response of respiratory minute volume to carbon dioxide are shown in Table I. All of the data are expressed as percentages of the normal response to the CO_2 challenge in each particular patient. The effect of CO_2 was consistently an increase in the tidal volume with very little change in the respiratory rate. The product of rate times tidal volume (minute volume) was used as the basis for the data in Table I. Accordingly, figures below 100 per cent indicate depression of the respiratory reaction to 5 per cent carbon dioxide in oxygen. Following the administration of meperidine alone, only two of the nine readings were 100 per cent or more of control values during the first 30 minutes. Two of the five determinations at 60 minutes were still depressed significantly, and one of the five values at 90 minutes was 89.3 per cent. It is, therefore, concluded that respiratory depression after meperidine, as it is used clinically, can be demon-

TABLE I

RESPIRATORY MINUTE VOLUME AFTER CARBON DIOXIDE CHALLENGE EXPRESSED AS PER CENT OF CONTROL RESPONSE TO CARBON DIOXIDE

	Patient	Meperidine (mg.)	Route	Minute volume (% of control)			
				15	30	60	90
(*a*) Meperidine alone	George B.	100	I.M.	—	82.3	110	—
	Jean M.	100	I.M.	—	64.6	71.7	104
	John J.	100	I.M.	—	77.7	75.7	109
	Claude W.	100	S.C.	84.8	105	96.1	97.2
	Sophie D.	50	S.C.	95.0	103	111	130
	George A.	50	S.C.	80.6	88.2	—	89.3
(*b*) 100 : 1	Claude W.	100	S.C.	113	131	117	113
	Sophie D.	50	S.C.	82.0	101	—	—
	George A.	50	S.C.	115	104	102	—
(*c*) 100 : 1.5	George B.	100	I.M.	—	105	115	—
	Jean M.	100	I.M.	—	103	116	126
	John J.	100	I.M.	—	96.0	117	143
	Claude W.	100	S.C.	117	102	128	103
	Sophie D.	50	S.C.	104	121	122	—
	George A.	50	S.C.	115	99.7	—	106
(*d*) 50 : 1	George B.	100	I.M.	—	114	132	—
	Jean M.	100	I.M.	—	151	129	128
	John J.	100	I.M.	—	109	98.6	—

strated as early as 15 minutes after injection and that this depression may persist for as long as 90 minutes after the drug was administered. It is self-evident from the data presented that the 50:1 mixture prevented respiratory depression. The 100:1.5 mixture was also effective in preventing respiratory depression since of 18 determinations only two were below 100 per cent, and these were of questionable clinical significance (96 per cent and 99.7 per cent respectively). Of the recordings for the 100:1 mixture, all except one are above control values. The 82 per cent reported for patient Sophie D. at 15 minutes is the lowest figure obtained for any mixture of meperidine-levallorphan in this study. This patient was in very poor condition on the day of this particular experiment. She had so much upper abdominal pain that her tidal volume was less than 200 ml. The other two patients did at least as well with the 100:1 mixture for the first 30 minutes as they did with the 100:1.5 ratio. We, therefore, conclude that a ratio of 100:1 provides protection against respiratory depression.

The values at 30 minutes for meperidine alone and the 100:1.5 mixture were submitted to an analysis of variance which is summarized in Table II. The results indicate that while there is no significance to the variance between subject responses, there is statistical significance ($P < 0.05$) to the variance between treatment effects.

The average pain relief for all treatments is summarized in Table III. These figures represent the average of all the observations for each period. All the drugs provided significantly greater analgesia than did saline. There was no appreciable difference in the analgesia produced by meperidine alone and the

TABLE II

SUMMARY OF ANALYSIS OF VARIANCE

Source	Degrees of freedom	Mean square	"F" ratio
Subjects	5	221.478	2.453
Treatment	1	943.570	10.451*
Error	5	90.284	

*$P < 0.05$.

TABLE III

AVERAGE PAIN RELIEF

	Average pain relief* (minutes)								
Treatment	15	30	60	90	120	150	180	210	240
Saline	0.3	0.5	−0.3						
Meperidine	1.2	1.5	1.4	0.7	0.7	0.5	0.3	0.3	0.3
Meperidine plus levallorphan 50 : 1	0.3	1.3	2.0	0.7	0.7	0.3	0.3	0.3	0.3
Meperidine plus levallorphan 100 : 1.5	1.3	1.0	1.2	0.7	0.7	0.5	0.5	0.3	0.3
Meperidine plus levallorphan 100 : 1	1.3	1.7	1.0	0.7	0.7	0.7	0.7	0.7	0.7

*0, no pain relief; 1, slight; 2, moderate. A negative number indicated that the pain was greater than it was at the start of the observation period.

combinations with levallorphan. We were somewhat surprised at the short duration of meperidine analgesia in three patients who failed to have further relief of pain 90 minutes after the injection. In one subject (George A.), however, analgesia persisted for four hours after meperidine alone and in combination with levallorphan.

Reactions to meperidine and the meperidine-levallorphan mixtures were recorded because it was of interest to know not only which ratio would provide analgesia without respiratory depression, but also which would produce the fewest number of untoward reactions. Table IV provides a summary of these observations. The number of reactions per patient was highest with the 50:1 ratio. There was no significant difference between meperidine alone and the 100:1.5 mixture. The ratio of 100:1 gave the lowest frequency of undesirable reactions. The very low incidence of nausea and the absence of emesis in this series are probably due to the fact that all the patients were in pain at the time the drugs were given and they were recumbent throughout the experiment. The effects of tolerance would also serve to reduce the number of reactions.

TABLE IV

NUMBER OF SIDE REACTIONS

		Meperidine: levallorphan		
Reactions	Meperidine	100 : 1	100 : 1.5	50 : 1
Sedation	2		1	2
Dryness of the mouth	1	1	2	
Excessive perspiration	2		2	3
Mental confusion	1		1	1
Headache				1
Tired	1	1		
Nausea	1			
Vertigo			1	
Total number of patients	6	3	6	3
Reactions per patient	1.3	0.66	1.2	2.3

DISCUSSION

Hamilton and Cullen (1), in an excellent clinical report on levallorphan, deliberately induced respiratory depression by the intravenous injection of narcotics in anaesthetized patients. They then gave levallorphan intravenously to overcome the depression. In thirty such cases, they used meperidine in doses of 25 to 450 mg. Our analysis of their data indicates that they used ratios of 25:1 to 300:1 with an over-all average ratio of 96:1. It would thus appear from their study and our own that a ratio of 100:1 is sufficient to prevent depression if both drugs are given simultaneously, and to restore respiration when levallorphan is given after the appearance of meperidine-induced depression.

This study demonstrates the value of studying drug effects on respiration by using the carbon dioxide technique. The burden that a drug places on the respiratory mechanism may not always be apparent if observations are limited to rate, tidal volume, alveolar CO_2 and oxygen. The respiratory system will compensate as best it can in order to maintain homeostasis and, therefore, tests for the adequacy of respiratory exchange reveal only the over-all results. Such tests do not indicate the load or burden upon the respiratory centre. For example, none of our subjects showed any respiratory embarrassment while breathing room air. However, the test with 5 per cent carbon dioxide revealed the depression of the respiratory centre, and uncovered the inability of the system to compensate for this additional stress. Clinically, this may imply a diminution in the patient's "reserve," and his lack of capacity to compensate as it relates to respiratory exchange. The clinical significance in anaesthesiology includes the necessity of allowing for this hidden depression whenever narcotic analgesics are used. For example, although the patient who is brought to surgery an hour after being given a narcotic may appear to have good respiratory function, the system is, in fact, already working under a handicap and may be very brittle in its response to inhalation anaesthesia. These same considerations apply in obstetrics when the mother is given a narcotic analgesic within an hour of delivery. Her respirations may be normal, but the child may have difficulty in overcoming the added burden of a depressed respiratory centre. These factors argue in favour of the use of a combination of narcotic analgesic and antagonist even when respiration appears normal, as a means of increasing the safety factor. The clinical usefulness of such combinations has been demonstrated by a number of investigators (2–6).

Although the data from the number of patients in this study may not lend themselves well to complete statistical analysis (with its mathematical expressions of probability and significance), it cannot easily be denied that there are clinical implications to be derived from very careful observations on a small selected group.

SUMMARY

Meperidine hydrochloride in doses of 50 and 100 mg. depresses the respiratory response to 5 per cent carbon dioxide in oxygen. This depression may be observed as early as 15 minutes and as late as 90 minutes after subcutaneous or intramuscular injection.

A mixture of meperidine hydrochloride and levallorphan tartrate in a ratio of 100:1 prevents this depression, does not interfere with analgesia, and does not produce more undesirable reactions than does meperidine itself.

RÉSUMÉ

Le but de cette étude est d'évaluer quelques-uns des effets du levallorphan sur l'analgésie et la dépression respiratoire produites par la mépéridine.

Pour réaliser cette expérience nous avons choisi comme sujets des malades dont les douleurs chroniques nécessitaient l'usage de narcotiques. On a donné à tous les sujets du sérum physiologique, de la mépéridine et deux doses de

mépéridine et levallorphan dans des épreuves successives: ainsi, chacun des malades devenait son propre contrôle sur une base de comparaison.

On a mesuré les effets sur la respiration en comparant les effets sur le volume minuté de l'inhalation de 5 pour cent de gaz carbonique et d'oxygène. L'analgésie a été appréciée et enregistrée à l'aide d'une échelle où 0 indique aucune douleur; 1, une douleur légère; 2, une douleur modérée; 3, une douleur intense.

Le chlorhydrate de mépéridine à la dose de 50 à 100 mgm. déprime la réponse de la respiration à un mélange de gaz carbonique de 5 pour cent et d'oxygène. On peut observer cette dépression aussi bien 15 minutes après l'injection sous-cutanée ou intramusculaire que 90 minutes après cette injection.

Un mélange de chlorhydrate de mépéridine et de tartrate de levallorphan dans une proportion de 100 pour 1 fait disparaître cette dépression, ne modifie pas l'analgésie et ne donne pas plus de réactions indésirables que ne le fait la mépéridine seule.

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METHITURAL SODIUM FOR THE INDUCTION OF PAEDIATRIC ANAESTHESIA[1]

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NERAVAL[3] BRAND OF METHITURAL SODIUM was administered to 225 paedriatic cases in a single injection for the induction of general anaesthesia. It was employed over a period of several months in all cases that would ordinarily receive a barbiturate intravenously. Patients receiving thiopental during the six months immediately preceding this investigation were used in making comparisons. The lack of randomization renders the data unsuitable for rigorous statistical evaluation.

Age of Patients

Methitural was used in all age groups whenever a vein was available for venapuncture or when a cut-down was running. Approximately 40 per cent of the patients were under five years of age; 20 per cent were under three years of age; and 10 per cent were under six months of age.

Distribution of Cases by Age

0–7 days	8
1 week–6 months	13
6 months–1 year	8
1–2 years	9
2–3 years	11
3–4 years	23
4–5 years	18
5–10 years	88
10–16 years	47
	225

Types of Surgery

Methitural was employed before all types of operative surgery. All but two of the intrathoracic group were thoracotomies for congenital heart disease.

Intracranial	14
Surgery of head & neck	40
T & A'S	26
Endoscopy	9
Intrathoracic	26
Intraabdominal	31
Cystoscopy	8
Orthopaedics	36
Superficial surgery (excluding head & neck)	23
Neurological investigation	6
Portal venography	6
	225

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Premedication

Atropine alone was used in the majority of cases. No premedication was employed for those patients receiving ethyl chloride–ether sequence for adenotonsillectomy and endoscopy. Chlorpromazine and promethazine were used in four cases, and Pacatal on two occasions.

Premedication

None	54
Atropine	153
Atropine & Demerol	12
Atropine & ataraxic	6
	225

Combinations of Agents

Methitural was used alone on one occasion. It was given as an immediately preanaesthetic hypnotic to 41 patients. The majority of patients received a relaxant, nitrous oxide–oxygen, with or without a volatile agent in addition to methitural.

Methitural

Alone		1
With ethyl chloride–ether		41
With relaxant, $N_2O:O_2$	25	
$N_2O:O_2$ and TCE	66	
$N_2O:O_2$ and ether	43	
$N_2O:O_2$ and Fluothane	33	
	—	167
With $N_2O:O_2$ and volatile agent		9
With succinylcholine and O_2		7
		225

Properties of Methitural

The properties listed below have all been noted in series of adult patients (1, 2, 3, 4, 5, 6, 7). Compared with thiopental, they are: (1) a more prolonged period for induction; (2) a relative potency of about 70 per cent; (3) an increased incidence of coughing, hiccoughing and sneezing during induction; (4) pain at the site of injection when concentrations greater than 2.5 per cent are used; and (5) a shorter duration of action characterized by a faster, clearer recovery, free from "hangover".

Clinical Observations

Experience with children has confirmed the observations made on adults and noted above.

(1) *Duration of induction.* Loss of consciousness was noticeably slower than that to which we have become accustomed with thiopental. In smaller children this constituted a drawback. The prolonged presence of a needle in the arm resulted in a number of patients becoming restless. As a result, physical restraint was sometimes required, and this in turn increased the degree of apprehension. In order to avoid this disadvantage injections at a more rapid rate were attempted with results noted in section 3 below.

(2) *Potency*. The average induction dose in this series was 5.3 mg./lb. as compared with 3.8 mg./lb. of thiopental used in similar cases. These figures give a relative potency of 72 per cent.

(3) *Respiratory irritation*. The effects of a slow induction with a 2.5 per cent solution were noted in section (1) above. Increasing the rate of injection resulted in a brief bout of coughing or sneezing in most cases. Coughing was also observed in eight of the ten patients that received a 5 per cent solution. In no case did coughing persist, nor did laryngeal or bronchial spasm occur. In two cases coughing was sufficiently forceful to dislodge the needle from the vein, necessitating a second puncture for the administration of a relaxant.

Hiccough was also encountered, lasting fifteen minutes in one case. On other occasions it was abolished either by the short period of apnea accompanying intubation or by a short period of hyperventilation.

Coughing, sneezing or hiccoughing occurred in a total of 23 cases, an incidence of 10 per cent. While these phenomena disturb the smoothness of the induction they do not constitute a serious contraindication to the use of methitural.

Spasm of the masseters was encountered once, and retching without vomiting on two occasions.

(4) *Painful injection*. Pain at the site of injection occurred in two patients. One patient receiving a 2.5 per cent solution had had multiple venapunctures in the same vein preoperatively. The other incident occurred during the injection of a 5 per cent solution.

(5) *Duration of action and recovery*. Statistically valid conclusions with respect to the duration of action of methitural relative to that of thiopental cannot be drawn from this study. The impression gained, however, was that methitural was relatively shorter in action. The evidence from the two largest and most nearly homogeneous groups in the series follows.

(*a*) The author's "routine" anaesthetic for cases not requiring abdominal relaxation has been a barbiturate induction with sufficient relaxant for either intubation or pharyngeal relaxation followed by nitrous oxide–oxygen–trichlorethylene by a non-rebreathing technique. The latter has been continued throughout operation unless tachypnoea has occurred. Ether, additional barbiturate, or Demerol has then been given as a supplement.

During the period of this study 123 patients premedicated with atropine alone were anaesthetized by the method outlined above for operations lasting between 60 and 90 minutes. Thiopental was used for 83 of the patients and methitural for

TABLE I

PATIENTS GIVEN A BARBITURATE: RELAXANT: N_2O:O_2:TCE

	Thiopental	Methitural
Number of cases	83	40
Supplemented	12	18
Unsupplemented	71	22
Average dosage (mg./lb.)	3.8	5.3
Relative potency (%)	100	72

40. Almost 50 per cent of the latter required some supplementation (Table I). In almost every case this was necessary during the first 20 minutes of anaesthesia. This result was in contrast to the small proportion of patients requiring supplementation following induction with thiopental. In the latter group the need almost never occurred during the first 45 minutes of anaesthesia.

In both the supplemented and unsupplemented groups there was a greater percentage of fully coherent patients five minutes following the termination of anaesthesia when methitural was used. The average recovery times in both groups were shorter when methitural was administered (Table II).

TABLE II

RECOVERY PERIOD FOR PATIENTS IN TABLE I

	Supplemented		Unsupplemented	
	Thiopental	Methitural	Thiopental	Methitural
Number of cases	12	18	71	22
Percentage awake within 5 minutes	30.0	50.0	37.5	71.0
Average recovery time in minutes	16.0	11.5	14.3	7.5

(*b*) Table III reveals the average duration of unconsciousness of a group of patients undergoing superficial procedures of short duration. Methitural was given to 26 patients, and thiopental to 25. Both groups received nitrous oxide–oxygen–trichlorethylene in addition to the barbiturate. Those receiving methitural had a shorter average period of unconsciousness.

TABLE III

	Thiopental	Methitural
Number of cases	25	26
Average dose (mg./lb.)	3.5	4.8
Average duration of unconsciousness in minutes	33.3	25.2

We believe that these results lend clinical support to the contention that methitural possesses a shorter duration of action than does thiopental.

A qualitative difference in the recovery from methitural anaesthesia has been claimed. The impression gained was that patients who received methitural had a more rapid return of full consciousness. Patients induced with thiopental frequently fall asleep after regaining consciousness and require rousing from time to time. This situation was unusual in the patients induced with methitural. Several older children who had previously received thiopental volunteered that they felt more alert when methitural had been used.

Methitural before Open Drop Anaesthesia

Forty-one children were given just enough methitural to induce sleep before proceding with open drop ethyl chloride–ether anaesthesia. The average dose ± S.D. was 3.15 ± 0.32 mg./lb. All patients were light enough to react to the ethyl chloride induction by exhibiting withdrawal reflexes. Laryngospasm, coughing and breath-holding were noticeably absent. There was no respiratory depression at this level of dosage, and stage III plane 2 anaesthesia was rapidly established. All patients regained their laryngeal and cough reflexes on the table. The recovery period was not prolonged and averaged 8.6 minutes. There was no memory of the inhalation induction.

Methitural for Portal Venography

During splenic puncture movement of the organ may result in laceration of the capsule and intraperitoneal haemorrhage. For this reason, apnoea of approximately 50 seconds duration is desirable for the recording of splenic pressures and the injection of radio-opaque dye for portal venography. The injection of 0.4 mg./lb. succinylcholine has been used to induce such periods of apnoea. Immediately preceding the administration of the relaxant unconsciousness has been produced in six patients with methitural in doses averaging 4.2 mg./lb. Five patients were fully conscious within five minutes of giving methitural. The sixth was fully conscious within eight minutes.

Methitural in Hypothermia

Patients induced with thiopental and subsequently cooled to 27–31° C. have in many cases failed to regain consciousness until rewarmed to 34–35° C. All cases subjected to hypothermia following induction with methitural have regained consciousness immediately following the termination of nitrous oxide–oxygen anaesthesia, even at 29° C.

Infants undergoing major surgery tend to become hypothermic. Several instances of prolonged recovery have occurred in the past when thiopental was used in this group. All infants induced with methitural have awakened immediately following the termination of anaesthesia at temperatures of 33–34° C.

The hypothesis is that methitural, unlike thiopental, is almost completely eliminated during the cooling period, and that there is little residuum to be metabolized during rewarming. We feel that this is an advantage, since the conscious patient is able to move about, cry and expand his lungs fully, and thus assist in the rewarming phase.

SUMMARY

Experience with methitural sodium in 225 children ranging from one day to sixteen years of age indicates that this agent may be safely administered to all age groups and for all procedures in which other barbiturates are not contraindicated.

The annoyances of induction are the same as those reported for adults: coughing, sneezing, hiccoughing, retching, and pain at the site of injection. The prolonged induction period was a disadvantage in some children who were apprehensive and restless.

Our experience lends clinical support to the contention that methitural has a shorter duration of action than does thiopental. This property offers some advantage to those patients who may become hypothermic during operation, either deliberately or incidentally. It is of no advantage in normothermic cases lasting longer than thirty minutes, but is of value in shorter procedures, particularly for out-patients.

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SPECTROPHOTOMETRIC DETERMINATION OF FLUOTHANE VAPOUR

WERNER KALOW, M.D.*

IN THE ORIGINAL EXPERIMENTAL WORK on Fluothane reported by Raventos (1), the vapour concentration was controlled by a dropwise addition of mercury into liquid Fluothane, thereby causing an overflow of known volume which was immediately vapourized. Later, Raventos (2) introduced a trichloroethylene bottle from a Boyle's apparatus. It was fitted with an extended scale to control the concentration of Fluothane vapour for anaesthesia. E. Falkner Hill (3) measured the output of this and a similar apparatus by weighing the Fluothane vapour. He pointed out that the concentration of Fluothane vapour decreased during the application, even if the valve setting remained unaltered, owing to the fall of temperature caused by the evaporation of Fluothane. A temperature-compensated vaporizer (Fluotec) has been constructed since. However, a rapid means of measuring directly the concentration of Fluothane in an anaesthetic gas mixture is still needed, particularly during closed-circuit anaesthesia. Therefore, we have measured the spectra of Fluothane in order to see whether optical methods can be used. Suitable absorption was found in the ultraviolet as well as in the infrared ranges. The ultraviolet absorption was then used for some measures of concentration.

METHODS

The spectra were measured with two Beckman Recording Spectrophotometers: Model DK2 was used throughout the ultraviolet, visible, and near-infrared region; Model IR4 was used to record the near-infrared and infrared spectra. The measurements from the two instruments overlapped in the range between 1.0 and 2.8 microns.

The absorption cells used for the determination of the spectra had a light path of 10 cm. Liquid Fluothane was introduced into the cells where it evaporated while the cells were closed. For measurements in the infrared, the cells contained only traces of air besides the Fluothane vapour. The ultraviolet spectrum was determined in air. The report on the intensity of the infrared absorption may be regarded as semi-quantitative. The measurements in the ultraviolet were repeated until reproducibility of the data was established. That is, even with great variations of technique, the spectrum was reproducible within ±1.5 per cent.

The absorption cell used for checking the output of an anaesthetic machine had a light path of 10 mm. It was a silica cell of the type commonly used in Beckman Spectrophotometers, that is, it measured 1 × 1 × 4 cm. A tightly fitting cover for the cell was cut from plexiglass. Two small holes of about 1 mm. diameter were drilled into corners of the cover. Into these holes, two pieces of plastic tubing fitted closely. Both pieces were roughly 5 inches long. One piece of

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tubing was pushed far enough through the hole to have its opening near the bottom of the cell, the other piece of tubing went just through the cover so as to have its opening near the top of the cell. As long as the tubing does not come close to the centre of the absorption cell, it does not interfere with the beam of light passing through the cell. The cell is placed into the spectrophotometer, the two pieces of tubing sticking out. The cell can then be flushed with gas. If there is enough gas available, and if the optical measurements are done while the flushing proceeds, small leaks in the system are immaterial.

Plastic bags developed for breath samples containing alcohol (4) were used for transporting samples from the operating room to the laboratory. These containers consisted of an upper end of a one-pound ether tin; a Saran bag[1] 5 inches wide and 12 inches deep was fitted snugly over the cut-off end of the tin where it was tightened with adhesive. Fluothane vapour disappeared very slowly from these containers; a 50 per cent drop of its concentration took 26 hours.

With the aid of adapters, such a container could be connected with the absorption cell. By pressing the Saran bag, the gas sample was flushed through the cell. After a minute of flushing with roughly 100 ml. of gas, the optical measurements were made.

RESULTS

The essential parts of the absorption spectra of Fluothane vapour are demonstrated in Figure 1. The greatest absorption occurs in the ultraviolet. There are numerous other peaks of absorption in the infrared which are not presented because they are small in comparison with those shown. Most of the omitted peaks lie between 1.6 and 7 microns. There was no absorption between 1.6 and 0.27 microns (= 270 millimicrons). This includes the visible range.

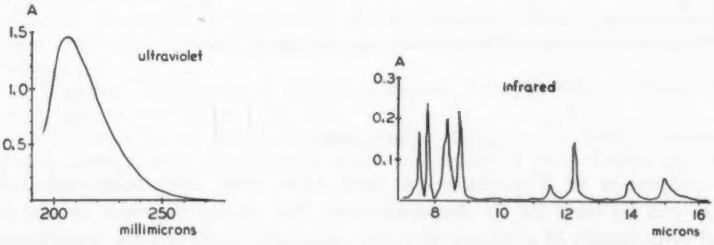

FIGURE 1. Ultraviolet and infrared absorption spectra of Fluothane vapour. Wave-lengths are given in millimicrons and microns. The letter A stands for Absorbance (formerly called optical density). Note the difference between the absorbance scales of the two graphs. The concentration of Fluothane vapour was 100 mg./l. The absorption cells had a light path of 10 cm.

[1] The bags were obtained from Mastex Ltd., 41 Torbarrie St., Toronto. The material was designated as "100 gauge double wound Saran." The bags were kindly mounted and checked by Mr. H. Salem.

The data are presented as mg. per litre because this is a measure independent of temperature and pressure. According to the definitions and figures of Hill (3), 100 mg./l corresponds to a concentration of 1.13 per cent. This measure of volume of vapour per volume of gas is the one most frequently used in practice. On this scale, the ultraviolet absorbance in a cell with 1 cm. light path of a gas, containing 1 per cent Fluothane, is 0.050 at 228 μ, 0.081 at 220 μ, or 0.141 at 206 μ.

Measurements at 228 μ need very little arithmetic for their interpretation. Furthermore, at this wave-length there is no interference with the measurements from anaesthetic gases. Nitrous oxide has an ultraviolet absorbance at shorter wave-length. Air or oxygen do not interfere at all in the indicated range.

Some analytical data obtained by ultraviolet spectrophotometry are shown in Table I. The output from a temperature-compensated vaporizer (TN Fluotec) was checked. The apparatus delivers very nearly the expected concentrations, apparently independent of the rate of gas flow. However, a slight drop of the output seems to have taken place during the seven minutes of sampling.

TABLE I

OUTPUT OF A TEMPERATURE-COMPENSATED VAPORIZER (FLUOTEC) MEASURED BY ULTRAVIOLET SPECTROPHOTOMETRY

Time of sampling (P.M.)	Rate of flow* in l./min.	Expected concentration of Fluothane (%)	Observed concentration of Fluothane (%)	Observed as % of expected
3 : 18	10	0.5	0.48	96
3 : 19	10	1.0	0.85	85
3 : 20	10	1.5	1.46	97
3 : 21	10	2.0	1.93	96
3 : 22	6	2.0	1.80	90
3 : 23	6	0.5	0.39	78
3 : 25	12	1.0	0.80	80

*The gas mixture was 50 per cent nitrous oxide in oxygen.

DISCUSSION

The properties of Fluothane are such that both ultraviolet and infrared radiation can be used for its demonstration. The choice depends on the availability of equipment. If a device is to be especially designed for monitoring the concentration of Fluothane during anaesthesia, utilization of the infrared absorption should be chosen. Simplicity and relative economy of the design can be achieved which is not possible in the ultraviolet. It is to be expected that commercial apparatus will soon be made available for this purpose. On the other hand, many laboratories are presently equipped for ultraviolet spectrophotometry, which has become widespread because of many other well-known biological applications. It has been shown that such available equipment is suitable for measurements of the concentration of Fluothane vapour.

SUMMARY

The optical properties of Fluothane vapour have been determined. There was a strong absorption of ultraviolet and infrared radiation. While the absorption in either range can be used to measure the concentration of Fluothane, quantitative data have been given only for the use of ultraviolet spectrophotometry. The construction of a suitable absorption cell, and a container in which Fluothane vapour can be transported, have been described.

ACKNOWLEDGMENTS

Dr. H. Cullumbine, Department of Pharmacology, and Dr. S. M. Campbell, Department of Anaesthesia, University of Toronto, suggested the problem to me. The anaesthetic apparatus was checked in co-operation with Dr. I. M. MacKay of the Department of Anaesthesia. Dr. G. F. Wright, Department of Chemistry, permitted the use of the infrared spectrophotometer.

RÉSUMÉ

On a fixé les propriétés optiques de la vapeur de Fluothane. On a noté une forte absorption de radiation ultraviolette et infrarouge. Bien que l'absorption dans les deux zones puisse servir à mesurer la concentration de fluothane, les données quantitatives ont été obtenues seulement avec l'emploi de la spectrophotométrie à l'ultraviolet. On décrit la construction d'une cellule d'absorption appropriée et un contenant dans lequel la vapeur de Fluothane peut être introduite.

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THE ESTIMATION OF FLUOTHANE* IN BLOOD†

J. G. Robson, F.F.A.R.C.S.(ENG.) and Peter Welt, M.D.‡

A METHOD for the estimation of Fluothane in blood was originally described by Goodall in an appendix to a report on the pharmacology of the drug by Raventos (1). The estimation consisted of the extraction of Fluothane from blood by petroleum ether and it was based on its hydrolysis by means of sodium amoxide, the released halides being estimated nephelometrically as the silver halide.

The method was modified by Duncan (2) who used lithium aluminium hydride as a reducing agent for the extracted Fluothane. He showed that lithium aluminium hydride would reduce Fluothane at room temperature, with the release of 80 per cent of the bromine and 30 per cent of the chlorine.

The following description contains some modifications of Duncan's method, dictated by practice, which simplify the handling process. An attempt is made to assess the accuracy.

Special materials required are: petroleum ether. (A.R.) B.P. 100–120 C.; silver nitrate solution, 0.01 N.; sulphuric acid, 50 per cent v/v.; anhydrous di-ethyl ether (A.R.); lithium aluminium hydride; ground glass stoppered test-tubes, 10 ml. capacity; 5.0 ml. syringes, recalibrated to deliver known volumes.

Preparation of lithium aluminium hydride solution (Duncan). Lithium aluminium hydride is used as a solution in di-ethyl ether, prepared by refluxing 500 mg. of the powdered reagent with 20 ml. of anhydrous di-ethyl ether for four hours, filtering through a No. 3 sintered glass filter and diluting the filtrate to 100 ml. with ether. The reagent keeps well if stored under nitrogen.

METHOD

Unknown Samples

A series of stoppered tubes is set up, each containing 6 ml. of petroleum ether. The blood samples, of 4 ml., are introduced into the liquid by means of a syringe and needle, care being taken to ensure that no air mixes with the blood. Samples in quadruplicate are used.

Preparation of Solutions for the Calibration Curve

A known solution of Fluothane in petroleum ether is prepared by weighing a graduated 50 ml. flask almost full of petroleum ether. About 200 mg. of Fluothane is dropped in, the flask is re-stoppered, inverted once or twice to absorb the Fluothane vapour in the neck and re-weighed. It is then filled to the mark with petroleum ether. The contents are well mixed and 5 ml. are removed by means

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*2-bromo-2-chloro-1-1-1-trifluoroethane.

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‡Wellcome Research Department of Anaesthesia, McGill University, Montreal.

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of a syringe and needle which are first washed out with the solution. This quantity is introduced into a 100 ml. graduated flask, almost full of petroleum ether and more petroleum ether is added to make up to 100 ml. Each ml. of the final solution then contains about 0.2 mg. of Fluothane.

A series of stoppered test-tubes is set up and 4 ml. of plain blood is placed in each with a syringe. Known volumes of petroleum ether and of the petroleum ether and Fluothane mixture, to a total of 6 ml., are added to make concentrations of from 0–1 mg. in 6 ml. of the solvent. These are best prepared in quadruplicate. As the resultant plot of optical density against Fluothane concentration is linear, the zero and two other points are adequate to establish the calibration curve.

Process

The tubes with the known and the unknown samples are treated together for the rest of the process in order to eliminate systematic error.

The tubes are rotated horizontally for thirty minutes held in clips on the rim of a wheel, to allow equilibration of Fluothane between blood and petroleum ether. They are then centrifuged to separate the layers. From each tube 5 ml. of the petroleum ether layer is taken with a syringe and needle and placed in another series of stoppered test-tubes. The second series of tubes must be scrupulously clean and dry, having been washed in distilled water. To each, 1 ml. of lithium aluminium hydride solution is added and the stoppers replaced, the tubes being shaken to effect mixing. The reduction takes place at room temperature and is allowed to proceed for twenty minutes. The excess reagent is then destroyed by the addition of 1 ml. of sulphuric acid; 5 ml. of distilled water is added and the tubes are shaken for one minute to dissolve the released halide. Then, 5 ml. of the aqueous layer is removed to a separate tube by means of a syringe fitted with a long stainless steel needle; 2 ml. of silver nitrate solution added, the tube is inverted once to mix and is placed in a dark cupboard for ten minutes. Shaking, or contamination with petroleum ether at this stage, will cause coagulation of the suspension of silver halide and give scattered results. The optical density to 520 mμ in a 1 cm. cell of this suspension is recorded. A calibration curve (see Fig. 1) is prepared from the results of the known solutions and the concentrations of Fluothane in the unknown samples are read directly from this. As the final dilution is the same for all the samples, the concentration found requires only to be multipled by 25 to give the concentration in mg./100 ml.

Assessment of Accuracy

In order to assess the accuracy of the method, standard solutions of Fluothane in blood were prepared as follows.

A very thin glass ampoule was weighed, some Fluothane was introduced into it, and then it was sealed and weighed again. The accuracy of weighing was ± 0.05 mg. The ampoule was placed in a bottle completely full of blood containing some short lengths of glass rod, the volume being determined previously. The bottle was shaken to break the ampoule and the contents thoroughly mixed for ten minutes. Quadruplicate samples were taken by means of a syringe and needle and treated in the usual way. A calibration curve was prepared at the same time.

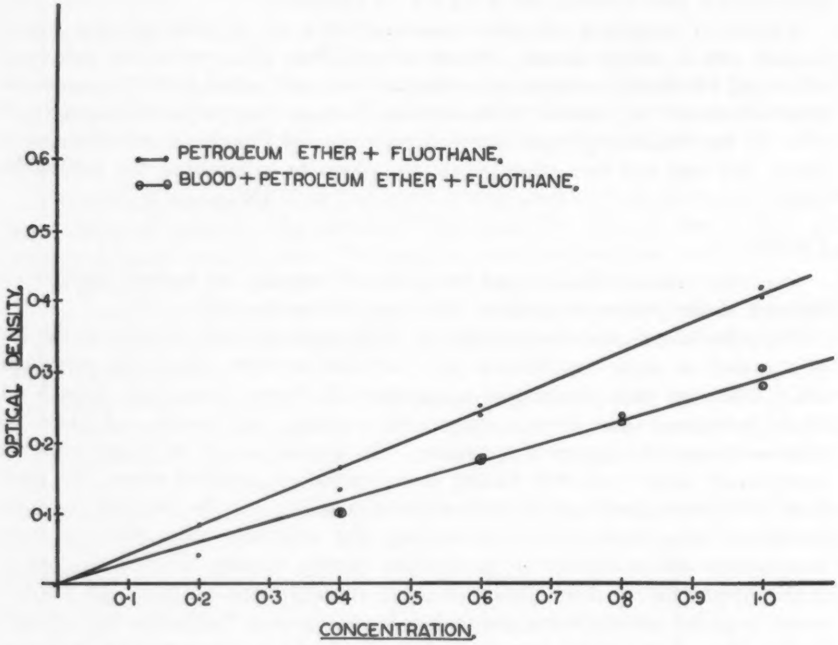

FIGURE 1. Vertical axis: optical density to 525 mμ, d_{1cm}; horizontal axis: concentration, mg./6 ml. petroleum ether.

RESULTS

Figure 1 shows two curves, one showing the results obtained with Fluothane and petroleum ether and the other with Fluothane, petroleum ether and blood. These were processed together as one batch.

They can be expressed as $y = bx$, b being the slope. The slopes, together with those of three other curves of each type are:

Fluothane and petroleum ether	*Fluothane, petroleum ether, blood*
.481	.356
.447	.344
.431	.306
.416	.294
Mean 0.444 ± 0.014	Mean 0.325 ± 0.015 ($P<0.001$)

Table I gives the results of eight known samples prepared and estimated as described. The standard deviation of the estimates from the observed values is

TABLE I

Fluothane mg./100 ml. blood		
Expected	Estimated	Difference (mg.)
18.45	15.70	−2.75
18.45	16.00	−2.45
18.45	17.85	−0.60
18.45	17.65	−0.80
18.63	18.65	+0.02
18.63	17.75	−0.88
18.63	18.65	+0.02
18.63	19.25	+0.62
19.70	18.75	−0.95
19.70	20.10	+0.40
19.70	19.25	−0.45
19.70	17.50	−2.20
22.20	22.00	−0.20
22.20	21.50	−0.70
22.20	22.00	−0.20
22.20	21.50	−0.70
13.66	12.75	−0.91
13.66	13.75	+0.09
13.66	14.25	+0.59
13.66	12.40	−1.26
15.30	14.37	−1.80
15.30	13.50	−0.93
15.30	14.15	−1.15
15.30	14.37	−0.93
15.55	15.25	−0.30
15.55	16.00	+0.45
15.55	15.40	−0.15
15.55	15.25	−0.30
11.17	8.90	−2.27
11.17	12.37	+1.20
11.17	11.75	+0.58
11.17	12.00	+0.83

± 1.14 mg. This standard deviation is given because a consideration of Figure 2 and Table I shows that, in the concentration range used, the accuracy is approximately the same at the high as at the low concentrations. This is due to the fact that the error appears to lie mainly in the measurement of the reagent which contributes an error independent of the concentration of Fluothane.

Discussion

In early trials the greatest inaccuracy was found to be in the variable extraction rate. If the blood and petroleum ether are shaken together, as recommended by Goodall and Duncan, sufficiently to ensure extraction of the Fluothane, an emulsion frequently forms or bubbles of petroleum ether become coated with some constituent of the blood, making it impossible to effect separation. We found that thirty minutes of slow rotation of the tubes gave the maximum extraction rate and avoided these difficulties.

Goodall and Duncan recommended the use of 4 ml. of petroleum ether for the extraction of 4 ml. of blood, with the removal of 3.5 ml. for the reaction. We found that the number of spoiled samples was then high as we frequently could not avoid drawing some plasma into the syringe in the effort to obtain 3.5 ml.

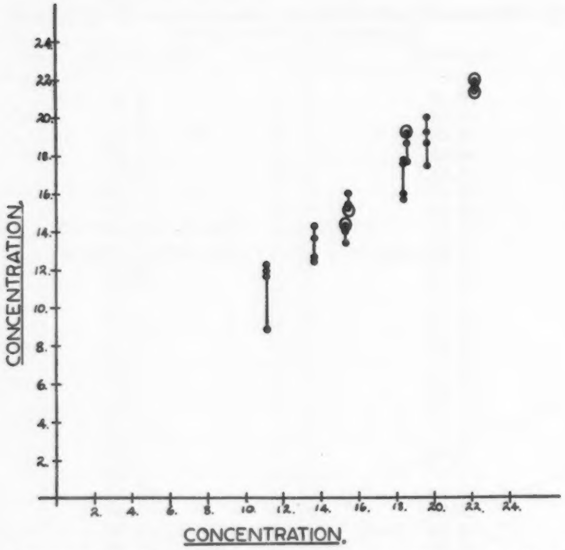

FIGURE 2. Vertical axis: estimated concentration, mg./100 ml. blood; horizontal axis: expected concentration, mg./100 ml. blood.

To use 6 ml. and to leave 1 ml., makes this easier and yet gives about the same proportion of Fluothane for the reaction.

The reagent alone is responsible for an optical density reading of between 0.07 and 0.09 which is dependent upon the batch of reagent and the volume used in the reaction. Great care has to be exercised in the precise measurement of its volume.

The activity of 1 ml. of lithium aluminium hydride solution is sufficient for the reduction of all the Fluothane likely to be found in 4 ml. of blood. When it was tested with high concentrations of Fluothane in petroleum ether it produced sufficient halide to give silver halide suspensions too dense to be estimated in a 1 cm. cell. The presence of water or plasma in the reaction tubes, by inactivating some of the reagent, produces low results.

The wave-length used by Goodall and Duncan was 520 mμ. There are, however, no interfering absorption bands and the peak at 520 mμ is not sharp. A simple null reading electrophotometer was used for this work with a filter peaking at 525 mμ.

The results show that there is a significant difference in the slopes of calibration curves prepared with and without blood. This is due to the retention of a quantity of Fluothane by the blood. The eventual equilibrium of Fluothane between blood and petroleum ether probably depends to a large extent upon the temperature at which this takes place because the slope of the calibration curve varies from day to day with any one batch of reagent solution. It, therefore, introduces considerable error to use a calibration curve prepared without blood. It is necessary to process the samples for the calibration curve and the unknown samples at the same time.

The method is sufficiently accurate for clinical investigational purposes.

SUMMARY

A modification of the methods of Goodall and Duncan for the estimation of Fluothane (2-bromo-2-chloro-1-1-1-trifluoroethane) in blood is presented.

It is shown to be necessary to construct a calibration curve for each batch of samples to be analyzed. For this purpose it is necessary to use known concentrations of Fluothane with plain blood.

The accuracy is assessed and is shown to be sufficient for clinical investigational purposes.

RÉSUMÉ

Nous avons présenté une modification des méthodes de Goodall et Duncan pour le dosage du Fluothane dans le sang.

Il est nécessaire de faire une courbe de calibration pour chaque groupe d'échantillons à analyser. Dans ce but il faut employer des concentrations connues de Fluothane avec du sang total.

La méthode est précise et suffisante pour fin de recherche clinique.

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CONCENTRATIONS OF FLUOTHANE VAPOUR PRODUCED BY VAPORIZING BOTTLES OF SOME STANDARD ANAESTHETIC MACHINES*

J. G. ROBSON, F.F.A.R.C.S. (ENG.), and PETER WELT, M.D.†

THE FIGURES SHOW the concentration of Fluothane vapour delivered by the vaporizing bottles noted on each figure, the conditions being stated.

The concentrations were estimated by means of a katharometer which was calibrated with known mixtures of Fluothane in oxygen with oxygen as the reference gas. The mixtures were prepared by vaporizing a known weight of Fluothane with a measured volume of oxygen into a fifty-litre polyvinyl chloride bag. The calculation to volume/volume was made with the assumption that the mixture was an ideal gas. The response of the katharometer was shown to be linear within the required range and it was therefore sufficient to use one known mixture and the zero to contruct the calibration curve for each test. The stability of the instrument was good. The average error of estimation was ± 1.8 per cent of the percentage stated. It is of interest to note that the concentrations given for these vaporizers, if corrected for the temperature change of the Fluothane liquid, show that the fall in temperature is almost solely responsible for the fall in

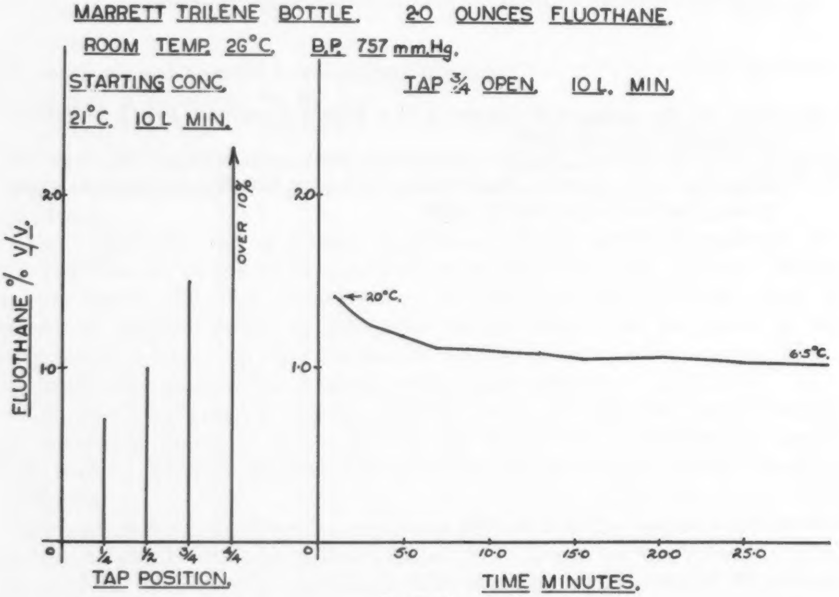

FIGURE 1

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†Wellcome Research Department of Anaesthesia, McGill University, Montreal.

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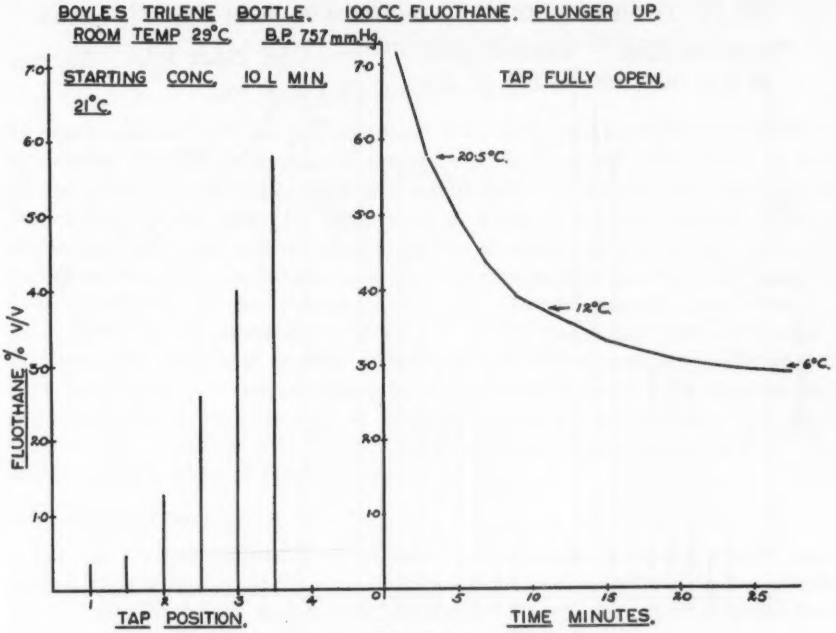

FIGURE 2

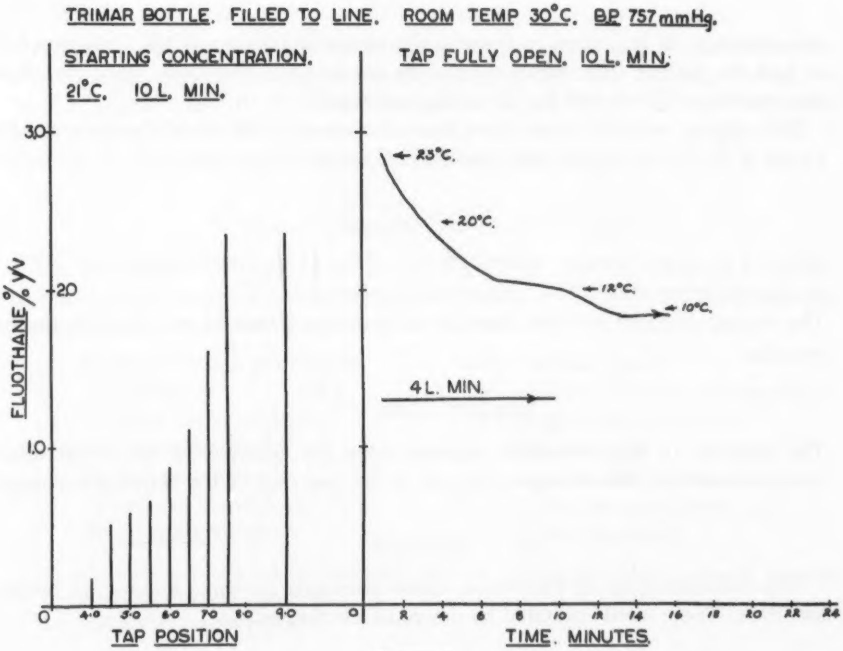

FIGURE 3

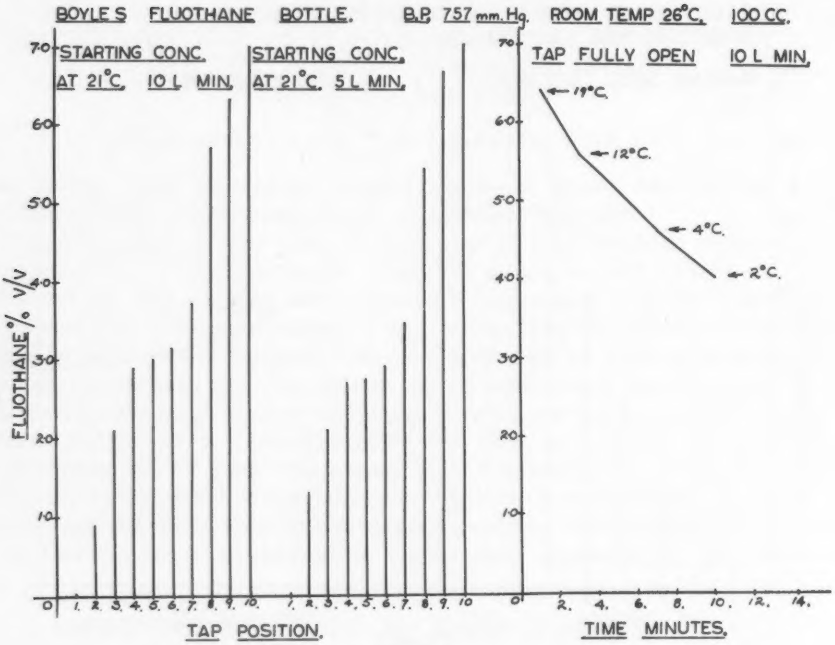

FIGURE 4

concentration. If one cares to insert a thermometer into the bottle, it is possible to find the issuing concentration from its reading and the curve, provided that the conditions of flow and the tap setting are similar.

The starting concentrations have been corrected to the stated temperature by means of the following formula (using 21° C. as the temperature):

$$C_{21^\circ} = C_{x^\circ} \frac{p_{21^\circ}}{p_{x^\circ}}$$

where C_{x° concentration estimated at x° C.; C_{21° concentration at 21° C.; p_{x° vapour pressure at x° C.; p_{21° vapour pressure at 21° C.
The vapour pressure p at the absolute temperature T can be calculated from the formula:

$$\text{Log}\, p = 7.732 - \frac{1564.}{T}$$

The accuracy of this correction depends upon the accuracy of the temperature measurement and the average error was ± 3.5 per cent of the stated percentage.

SUMMARY

The concentrations of Fluothane vapor produced by some vaporizing bottles are given. These were estimated by means of a katharometer.

PACATAL* IN CARDIO-PULMONARY SURGERY

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IN THEIR RESEARCH on the phenothiazine derivatives, workers have endeavoured to develop substances of greater potency and less toxicity. One result of such pharmacological researches was the introduction of Pacatal in Germany by Nieschulz *et al.*, in 1954 (1). Since then, its value as a potent ataraxic (that is, a quieting drug that relieves the symptoms of emotional and mental perturbation characterized by agitation, insomnia and preoperative anxiety) has definitely been established. In cardio-pulmonary surgery, Pacatal has also been described as an intravascular anaesthetic of the heart (2–5), and it is reported to prevent or favourably influence cardiac arrhythmias in thoracic surgery. Gifted with such properties, this new ataraxic, Pacatal, deserved more exhaustive studies, experimentally on dogs as well as clinically on man. Consequently, this paper presents the results of five hundred different observations made on fifty dogs and a hundred cases of thoracic surgery on man.

Chemistry and Supply

Pacatal (N-methylpiperidyl-(3)-methyl phenothiazine) is a synthetic compound. It is available in 25 and 50 mg. tablets in the form of hydrochloride, for oral administration, and in 2 cc. ampoules (25 mg. per cc) and in the form of the more soluble acetate, for parenteral use.

Toxicity

According to experiments made by other workers (1), in an exhaustive study on the chronic toxicity of Pacatal, daily doses of 5 mg./kg. during two months, did not modify the blood formula of dogs (red and white blood count and haemoglobin). Furthermore, repeated injections of the useful dose of Pacatal are given to dogs without noticeable toxic effects.

PACATAL IN EXPERIMENTAL CARDIAC SURGERY

For this study, we drew on a pool of fifty dogs, and experiments were conducted, in fifty sessions during which five hundred observations were recorded under the following headings:

(1) O_2 consumption per minute
(2) Temperature
(3) Femoral blood pressure
(4) Electrocardiography
(5) Electromanometry
(6) Pulmonary ventilation
(7) Blood constituents
(8) Cardiac output
(9) Sedative and potentiating effect
(10) Antifibrillating effect in hypothermia
(11) Anti-swelling action
(12) Action on sympathetic and parasympathetic

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*Pacatal ampoules and tablets necessary for this study have been graciously furnished by Warner-Lambert Canada Limited.

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The fifty sessions consisted mostly of heart surgery, such as the Blalock operation, the production of mitral insufficiency, and the combined production and repair of inter-auricular defects (gross method).

Anaesthetic Technique

Before discussing the results of these different studies, let us specify that most of these dogs weighed 30 to 40 kg., and that Pacatal was given on the basis of 5 mg./kg. body weight either orally or parenterally.

The dogs were all anaesthetized in the same fashion. After a premedication of morphine and Pacatal, anaesthesia is induced with sodium pentobarbital I.V., 25 to 30 mg./kg. body weight. As soon as the dogs were unconscious, they were intubated with a catheter equipped with an inflated cuff and pure oxygen was given. At the opening of the thorax respiration was controlled by a spiropulsator with positive pressure.

Discussion

Generally speaking, it will appear that the resulting experimental data are consistent with those of other pioneer workers on Pacatal (9).

(1) *O_2 consumption per minute.* There were 42 observations made on 24 dogs in the course of 25 experimental sessions, one of them being used at two sessions:

No. of sessions	*No. of dogs*	*No. of readings each*	*No. of observations*
10	10	1	10
12	11	2	22
2	2	3	6
1	1	4	4
25	24		42

Pacatal was found to exercise a minimal effect on the basal metabolism because there was only the slight decrease of 10 per cent and that in only 75 per cent of the cases.

(2) *Body temperature.* In 20 sessions on 20 different dogs 70 observations on possible temperature variations were made.

No. of dogs and sessions	*No. of readings each*	*No. of observations*
4	1	4
3	2	6
6	3	18
7	6	42
20		70

The antipyretic properties of Pacatal are nil and there was no modification of the thermal curve during the interventions other than the expected slight hypothermia of a few degrees due to anaesthesia and thoracotomy.

(3) *Femoral blood pressure.* The hypotensive effect of Pacatal is relatively weak. Only in large doses, such as 20 mg./kg. body weight intravenously does it bring about a noticeable but fleeting decrease in the dog's blood pressure. In the course of continuous recording of femoral blood pressure a decrease of about 5–10 mm. Hg only is noticed.

No. of dogs and sessions	*No. of readings each*	*No. of observations*
3	1	3
6	2	12
3	3	9
12		24

(4) *Electrocardiography and antifibrillating effect.* During experimental cardiac surgery the electrocardiograph remained stable in most cases when Pacatal was used.

No. of dogs and sessions	*No. of readings each*	*No. of observations*
5	1	5
2	2	4
7	3	21
1	4	4
3	5	15
2	6	12
1	9	9
1	10	10
1	12	12
1	13	13
1	26	26
25		131

A few dogs showed readily reversible minor alterations and an incidence of only 9.8 per cent of ventricular fibrillation occurred in this series as compared to 50 per cent in a previous series (6) when Pacatal was not used. In provoked hypothermia, Pacatal made it possible to apply vascular clamps for 22 minutes at 28° C. without precipitating fibrillation.

A refinement in evaluating the epicardial and endocardial excitability at the ventricular and auricular levels was made possible by scheduling a series of seven tests: (1) pressure under the axial edge of the left auricle, at the emergence level of the left coronary artery, (2) pressure on the medial edge of the right auricle, near the orifice of the superior vena cava; (3) pressure on the trunk of the left auriculo-ventricular artery, distal to the 2nd or 3rd collateral; (4) pressure applied with instruments on the posterior surface of the heart behind the apex; (5) pressure with the tip of the index finger across the infundibulum of the ventricle, on the anterior papillary muscle of the tricuspid; (6) the invagination of the index finger, forcing back the left auricle into the mitral orifice, partially blocking it, and into the left ventricular cavity itself; (7) the invagination of the index in the left ventricle with the left hand exerting counter-pressure either on the thoracic wall or on the right cardiac surface.

On dogs prepared with Pacatal (5 mg./kg. body wt.) each test was executed while recording with an electrocardiograph. Presently, certain alterations of conduction and rhythm occurred, but contrary to what happened in the absence of Pacatal (11), when the cardiac excitement ceased, the return to normal tracings on the electrocardiograph was immediate. Thus, the great protection of Pacatal was demonstrated in permitting such rapid reappearance of the sinus rhythm after these surgical manœuvres of cardiac irritation and in hindering the appearance of prolonged anomalies of conduction and rhythm such as cardiac blockage and ventricular fibrillation. Also, with Pacatal, the galvanic and faradic excitement of the heart did not produce prolonged abnormal patterns of cardiac rhythm or conduction and the sinus rhythm always reappeared once the excitement was over. The authors (2–5), therefore, have reasons for describing the action of Pacatal as that of an intravascular anaesthesia of the heart. However, in the course of certain surgical manœuvres (e.g., the production and repair of an inter-auricular communication (Gross method)) Pacatal does not appear to protect the heart from all reflexes, particularly the twisting reflexes in placing the well of Gross.

(5) *Electromanometry*. The intra-cardiac pressures were recorded with the Sanborn electrocardiomanometer.

No. of dogs and sessions	*No. of readings each*	*No. of observations*
2	1	2
6	2	12
4	3	12
2	4	8
1	5	5
1	11	11
16		50

On the Sanborn electrocardiomanometer, the different curves of intra-cardiac pressures, auricular and ventricular, right and left, were absolutely comparable to the curve of the femoral blood pressure registered on the Ludwig manometer, and recorded on a smoked cylinder: that is, the intra-cardiac pressure decreased in 40 per cent of the cases by only 5–10 mm. Hg.

(6) ***Pulmonary ventilation*** (using Collin's Spirometer). In all the dogs, the intravenous injection of Pacatal (5 mg./kg. body wt.) provoked an increase in the ventilation per minute at rest. There was an increase, either in the frequency of breathing or in the tidal air, or in both. Pacatal, therefore, did not depress the respiration. This is an essential property of a good drug in pulmonary surgery.

No. of dogs and sessions	*No. of readings each*	*No. of observations*
1	1	1
9	2	18
10	3	30
20		49

Interestingly, a similar experiment with chlorpromazine always provoked a fall in intra-cardiac pressure on the electromanometer (11).

(7) *Cardiac output* (*Fick*). In the course of the 12 experiments on 12 different dogs, the cardiac output was measured once on each. Also, with Pacatal, the cardiac output of our dogs remained stable in 50 per cent of the cases, and we noted a slight decrease in the other 50 per cent. This latter fall was attributable to the modifications in the minute oxygen consumption.

Here again, we note that similar previous experiments with chlorpromazine have always shown a lowered cardiac output in all the cases (11).

(8) *Blood constituents.* Towards the end of 10 experiments on 10 different dogs a blood sample was analyzed and no notable modification was found.

(9) *Sedative and potentiating effect.* In all 50 dogs the sedative and potentiating effect of Pacatal was quite noticeably shown by the co-operative behaviour of the subjects. In fact, even the most distraught and ill-tempered animals complacently submitted to venoclysis for anaesthesia induction when the combination morphine-Pacatal was used as premedication. The doses of morphine were gr. ⅛ for dogs under 50 lb. and gr. ⅙ for those over 50 lb., and those of Pacatal the usual 5 mg./kg. body weight.

(10) *Anti-oedema effect.* A vain attempt to provoke acute pulmonary oedema was made on two dogs which had received Pacatal by rapidly injecting 20 cc. of hypertonic saline intravenously.

(11) *Action on sympathetic and parasympathetic nervous systems.* The vagolytic action of Pacatal was demonstrated by the absence of hypotension and of bradycardia after galvanic stimulation of the distal cut end of the vagus nerve. Its sympathicolytic action is shown by the inhibition of the sino-carotid reflex and by the contraction of the nicitating membrane after galvanic stimulation of the cervical preganglionic sympathetic fibres.

PACATAL IN PULMONARY SURGERY

We now pass on to the use of Pacatal in man, and more particularly in thoracic pulmonary surgery. Proving to be a powerful ataraxic and a well-balanced neuroplegic, Pacatal soon came into routine daily use in our thoracic surgery centre. For the last six or eight months, it has been regularly administered to all our thoracic cases.

Anaesthetic Technique

The present study is based on the use of Pacatal in a hundred cases of pulmonary surgery chosen at random, and including segmentectomies, cuneiform resections, lobectomies and pneumonectomies. The average age of the patients was 33 years, the youngest being 10 years old, and the oldest 60. In remote premedication, 36 to 48 hours before operation, we use Pacatal in anxious patients where the usual sedatives are inadequate to alleviate the preoperative anxiety. To these patients doses of 100 mg. are administered orally, three times a day, without side effect other than dryness of the mouth and a slight degree of constipation. In the event of too marked an effect, the dose is simply temporarily reduced. Moreover, with Pacatal, we are always successful in quieting the most anxious patients and we note here an advantage it has over chlorpromazine. With Pacatal, as it is but slightly hypotensive, it is unnecessary to keep the patients in bed.

In immediate premedication, we use Pacatal routinely on all patients, because of its neuroplegic properties; potentiation of sedatives and anaesthetics, and cardiac protection. Pacatal is then administered intramuscularly in doses of 50 to 100 mg., immediately before the operation (i.e., a half-hour before the operation time proper). If need be, in the course of anaesthesia, during long surgical operations, a supplement of Pacatal is injected intravenously at the rate of one-half the initial dose (25–50 mg.). It is our experience that the best practical total dose of Pacatal given as premedication plus that given during operation can be satisfactorily calculated about the round figure of 1 mg./lb. body weight. (example: a 150 lb. patient may receive 100 mg. preoperatively and the remaining 50 mg. during operation). Of course, this schedule is tentative and must be adapted to the individual patient. On awakening, Pacatal is again given intravenously or intramuscularly 25 mg. at a time, to control agitation or vomiting. Finally, in the postoperative period, Pacatal is sometimes prescribed to control operative "stress" in the few excessively nervous and anxious patients. Pacatal is not an analgesic in itself and can, therefore, be prescribed in association with other sedatives.

Discussion

Following the example of Huguenard and Laborit (10), we believe that the ganglionic blockade of the neuro-vegetative system can diminish and even suppress the risks of shock caused by the stimulation of regions rich in adrenergic fibres (sympathetic, periaortic and cardiac plexuses, phrenic and splanchnic nerves) found in the thorax, and which are subjected during thoracic interventions to all sorts of aggressions. Pacatal actually provides a well-balanced ganglionic blockade in keeping equilibrium between sympathetic and parasympathetic. It ensures the heart a protection, which, though imperfect, has until now been impossible. And if we admit that parenchymatous and bronchial complications of thoracic operations often have a neuro-vegetative cause, and that a vagosympathetic disequilibrium is involved in the origin of atelectasis, we must agree that the use of a well-balanced ganglioplegic such as Pacatal would guarantee smoother postoperative periods.

From our experience with Pacatal, in more than a hundred patients undergoing pulmonary surgery, we are inclined to believe that this new phenothiazine derivative improves the peripheral circulation during operation. Pacatal diminishes capillary permeability, so that there is less operative shock and less venous stagnation, especially in the face-down position on the Overholt table. Pacatal reduces the incidence of arrhythmia during operation and, consequently, the incidence of cardiac arrest. (There were none in this series as compared to an incidence of 2 per cent of cardiac arrests in a previous unpublished study of 500 cases at this hospital). Pacatal reduces by about 10 per cent the doses of curarising agents and anaesthetics: 900 mg. of barbiturates instead of 1,000 mg. and over, for a 3½-hour operation. In addition to barbiturates, nitrous oxide–oygen is adminstered alone with the necessary curarising agents.

Pacatal slightly reduces bleeding during operation (an average loss of 900 cc. in our 100 pulmonary resections). This can be compared to an average blood loss of 1,500 cc. in a previous series of 119 pulmonary resetions (12). Of course, Pacatal is not the sole factor since it is highly probable that improved surgical techniques are also contributing.

In this series not one patient developed postoperative oedema where Pacatal was used. In the previous series of 500 cases mentioned above I remember of a few patients with oedemas, some of which were caused by postoperative overloading.

In that previous series of 500 pulmonary resetions there was a 16 per cent incidence of postoperative atelectasies, whereas in this present series only 8 per cent needed bronchial aspiration.

However, as mentioned above, the lower incidence of complications in the present series, interesting as it may be in relation to Pacatal, is attributable to improved techniques as well as to the drug used.

CONCLUSION

The potentiated anaesthesia with Pacatal in cardio-pulmonary surgery certainly presents advantages, above all in regard to cardiac protection: absence or marked reduction of ventricular fibrillation in experimental cardiac surgery in dogs, and absence of arrhythmia and cardiac arrest in thoracic pulmonary surgery in man. Moreover, the 500 different studies made on dogs clearly demonstrate that Pacatal is not a dangerous drug. Many times the effective dose of Pacatal has been injected in dogs without any toxic effect. Femoral and intra-cardiac pressures and cardiac output are very slightly changed, as are the blood constituents. Finally, in the remote premedication for anxious subjects, Pacatal is probably the ataraxic that can be prescribed with the minimum of danger and the maximum of efficiency.

Pacatal, therefore, ensures a better preoperative sedation, a smoother induction of anaesthesia, a more effective cardiac protection, a quieter postoperative period and has a marked anti-secretory effect. For all these reasons, in our opinion, Pacatal can certainly take an enviable place in the therapeutic arsenal of the surgeon and of the thoracic anaesthetist.[1]

ACKNOWLEDGMENTS

I wish to express my gratitude to the surgeons of Laval Hospital and particularly to Dr. Fernando Hudon, professor of anaesthesia, for his authoritative guidance.

[1] Since the preparation of this work, we have used "Pacatal" on some twenty other patients in the pulmonary clinic, as well as in some fifteen other experiments on dogs, and we have obtained results identical to those reported in the above series.

RÉSUMÉ

L'anesthésie potentialisée au Pacatal en chirurgie cardio-pulmonaire présente certainement des avantages, surtout en ce qui regarde la protection cardiaque: absence ou réduction marquée de la fibrillation ventriculaire en chirurgie cardiaque expérimentale chez le chien et absence d'arythmie et d'arrêt cardiaque chez l'homme en chirurgie thoracique pulmonaire.

De plus les 500 études différentes faites chez le chien démontrent clairement que le Pacatal n'est pas un médicament dangereux; chez le chien, la dose utile de Pacatal a été plusieurs fois injectée sans effets mocifs.

Les pressions artérielles fémorales et intracardiaques, le débit cardiaque sont peu modifiés, et il en est de même de la formule sanguine. Enfin, cliniquement, en prémédication éloignée chez anxieux, le Pacatal est probablement l'ataraxique qu'on peut prescrire avec le minimum de danger et le maximum d'efficacité. Voilà pourquoi, à notre avis, le Pacatal peut certainement prendre une place enviable dans l'arsenal thérapeutique du chirurgien et de l'anesthésiste thoracique.

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DEVELOPMENT OF THE NEWER THIOBARBITURATES USED IN ANAESTHESIA

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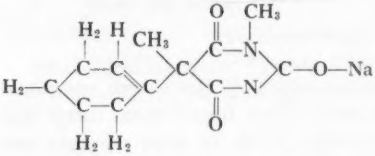
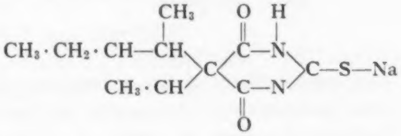
A REVIEW of the history of intravenous anaesthesia makes us wonder why such a method, which started only thirty years (1872) after the successful administration of ether anaesthesia by Long (1842) and Morton (1846), did not become more generally accepted until twenty years ago; and why such a method did not start earlier, when intravenous injection of fluids was first reported about two centuries before that, in 1651 (1). Its slow progress in the past was not due so much to a failure to appreciate its value as to the lack of suitable and effective agents (2). For that same reason, the search for better agents continues to the present, in spite of the fact that thiopental seems to be enjoying universal acceptance.

A number of drugs have been administered intravenously for the production of general anaesthesia. None proved completely satisfactory until two rapidly acting barbiturates, hexobarbitone (3) and thiopental (4) were introduced. These two substances started a resurge of interest in intravenous anaesthesia.



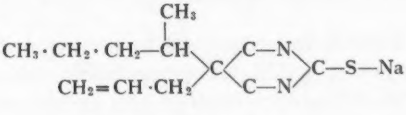
Sodium Hexobarbitone (Evipal)



Sodium Thiopental

The advantage of intravenous anaesthesia is well established. However, the agents in use are not ideal (2). They have undesirable effects on the respiratory and parasympathetic systems, aside from their cumulative action (5). Some barbiturates possess definite stimulating properties, sometimes restlessness and twitching persist throughout the whole course of action making them unsuitable for use as hypnotics. Stimulating properties of barbiturates show also as laryngospasm during the introductory phase of intravenous barbiturate anaesthesia (6).

Lund reported his experience with thiamylal sodium (Surital Sodium) (7).



Thiamylal Sodium (Surital)

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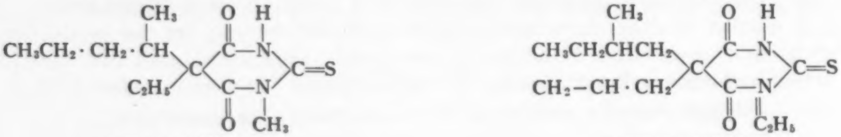
This did not gain popularity as it did not show convincing advantage over thiopental.

Several hundred N-methyl nitrogen barbituric acid derivatives were synthesized, hoping that the replacement of the oxygen by sulfur and alkylation of nitrogen might produce a drug of shorter action than thiopental. Unfortunately, the shorter duration is accompanied by frequent untoward side effects. The toxicity and duration of 4-N-methyl derivatives were found similar to thiopental and thiamylal in the same species (8). It was also shown that they have less cumulative action than their parent thiobarbiturates, suggesting a more rapid rate of breakdown. Stoelting and others (9, 10) studied five of these drugs clinically. They reported that two of these drugs (no. 14694) N-methyl thiopental and (no. 16193) N-ethyl thioseconal appear to produce hypnosis without undesirable side effects—contrary to the accepted theory that all N-methyl barbiturates display convulsive or even excitatory properties.



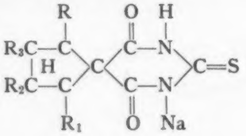
DRUG NO. 14694 DRUG NO. 16193

N-METHYL AND N-ETHYL THIOBARBITURATES

The use of others of this group was discontinued owing to the severe complications encountered (hiccoughs, laryngospasm, etc.). They found these drugs had half the duration of action of thiopental in dogs, while in man narcosis was extremely profound and of very brief duration. Papper and others (11) have shown that the shorter duration of N-methyl thiopental compared to thiopental is due to its greater affinity for body fat.

Sodium N-ethyl 5 allyl 5′ (2 methyl butyl) 2-thiobarbiturate is less potent in man than is methyl-thiopental. Other compounds have been tried, but the incidence of side effects such as laryngospasm and hiccoughs and occasional hypotension was so great as to exclude the possibility of them being of any clinical value.

In 1950, fifty spiro-barbituric acid derivatives and trials of the four "promising compounds" were reported by Swanson and others (12).



No.	R	R_1	R_2	R_3
14	CH_3	C_2H_5	H	H
18	C_2H_5	C_2H_5	H	H
26	CH_3	CH_3	H	CH_3
36	CH_3	C_2H_5	H	CH_3

SPIRO-THIOBARBITURATES

Typical anaesthetic effects were observed when two substitutes were introduced into the alicyclic ring of spiro-butane, spiro-pentane and spiro-hexane derivatives. The four spiro-thiobarbiturates were studied and reported to be effective anaesthetic agents. Occasionally however, recovery was slightly slower than following thiopental; retching, hiccoughs, coughing and muscle tremor occurred more frequently with nos. 18 and 26. Like thiopental, all four lowered blood pressure, increased pulse rate, depressed respiration, but did not inhibit vagal response to electrical stimulation. Volpitto (13) used a spiro-thiobarbiturate (Spirothal) (spiro-2-ethyl-3,5-dimethyl cyclopentane-5,5-pyramidine-2-thio-4,6-dione sodium) with decamethonium for endotracheal intubation. A rather high incidence of laryngospasm and bronchospasm was reported with this combination.

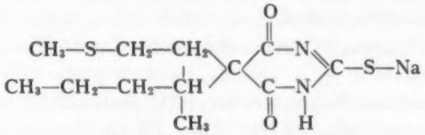
Because none of these drugs showed conclusive evidence of improvement over thiopental, other drugs are presently being investigated.

METHITURAL SODIUM (NERAVAL® SODIUM)

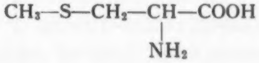
About two years ago, a new ultra-short acting intravenous anaesthetic with significantly more rapid recovery and fewer side effects than thiopental and thiamylal sodium was reported by European investigators. This drug, methitural sodium (Neraval Sodium) is known as "Thiogenal" in Europe.

Chemistry

Methitural sodium (Neraval Sodium)—sodium 5 (1 methylbutyl) 5-2-(methylthio) ethyl-2 thiobarbiturate is unique because of the presence of the methylthioethyl radical (CH_3-S-CH_2-CH_2), which is a radical found in methionine—an essential amino acid, important in the process of detoxification (14) and once used to reduce to the mininmum protein catabolism during anaesthesia (15). This explains its ultra-short action; due to rapid destruction and elimination by liver and kidneys.



METHITURAL SODIUM (NERAVAL SODIUM)



$$CH_3-S-CH_2-\underset{\displaystyle NH_2}{\underset{|}{CH}}-COOH$$

METHIONINE

Physical Properties

It is a pale yellow, hygroscopic powder buffered with anhydrous sodium carbonate. It has a pH about 9.8 and is compatible with Flaxedil, d-tubo curare and succinylcholine.

Pharmacology

The anaesthetic potency is two-thirds that of thiopental. Given in equivalent doses there is more rapid recovery. Cumulative action is negligible as compared to other drugs. It appears to have no synergistic action with atropine, morphine sulphate, succinylcholine or d-tubo curare.

Respiratory system. Spasm, cough and hiccough were found to be frequent when the drug was given in high concentration (5–10 per cent solution). Similar findings occurred when this drug, though more dilute was given rapidly. None occurred when 0.5 per cent drip with nitrous oxide and oxygen was used. Dillon and co-workers (14) reported that there was more salivation with Neraval than with thiopental. They state that its action is more parasympathomimetic than those of other barbiturates. Houde and others (16) showed that the introduction of an oro-pharyngeal airway did not give rise to any reflex disturbance even at light stages of anaesthesia. Erwin and co-workers (17) advocate premedication to include atropine because it appears to diminish or abolish salivation and coughing and seems to potentiate the depth and duration of anaesthesia.

Circulatory system. A report by Houde and co-workers (16) states that the systolic blood pressure drops 20–30 mm. Hg while diastolic remains unchanged; the pulse rate increases with this fall of blood pressure then returns quickly to normal. There occurs a generalized vasodilation as with other barbiturates. The colour of the skin remained normal and erythema was not seen. They considered that surgical haemorrhage was not more pronounced than usual, on the contrary, it seemed less. Whether this was due to the hypotension was not mentioned.

Riffin and Black (18) made electrocardiographic studies on patients given Neraval. The electrocardiogram was recorded during induction in fifty unselected cases. The changes compared favourably with those seen during thiopental or thiamylal anaesthesia.

Central nervous system. There were no chills, convulsions, mydriasis or agitation observed by Houde and others (16). They found that recovery was rapid and complete. There was no vertigo.

The drug has been used for electroconvulsive therapy (19). It was then reported that muscle rigidity may result, being most easily detected in the lower jaw and upper extremities. This was followed by varying degrees of muscle relaxation depending on the depth of anaesthesia. It did not alter the convulsive threshold. However, it influenced the type of seizure in that there were less intense tonic contractions and clonic movements which latter terminated abruptly. It appeared to shorten the period of seizure but not the period of post-seizure apnoea. Most important, they found that the recovery time was minimal. There was no hangover and the patients left the office within 20 minutes; when other barbiturates were given, the patients did not leave before 45–90 minutes. They mentioned that patients with asthma, severe hypertension or hypotension, mild cardiac decompensation and extreme obesity withstood the treatment well under anaesthesia.

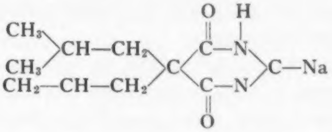
All seem agreed that the side effects are less when concentrations less than 5 per cent are used, and most advocate the use of dilute solutions for procedures lasting more than half an hour.

BUTHALITONE SODIUM

Another thiobarbiturate that is being investigated is ***transithal*** (Baytinal, Buthalitone). This was first described by Miller *et al.* (20) in 1936 and its pharmacology was investigated by Weese and Koss in experimental animals (21).

Chemistry

It is sodium 5-allyl-5′ isobutyl barbituric acid.



BAYTINAL (TRANSITHAL, BUTHALITONE)

Physical Properties

It is a yellowish powder with a slight smell, easily soluble in water. It is alkaline and is clinically used as a 10 per cent solution.

Pharmacology

Weese and Koss claimed the drug to be superior to other thiobarbiturates regarding its rapid recovery; however, they found it less potent. They found a dose of 500 mgm. was necessary to induce anaesthesia. Although most investigators emphasize its ultra-short action, Nobes (22) mentioned after his series that "delayed recovery is a drawback and therefore the drug cannot be unreservedly recommended for routine use." On the other hand, he says if it is used for induction and supplementary nitrous oxide is used, a smooth and rapid recovery can be predicted far more confidently than with other intravenous agents used in the same way. He mentions that postoperative drowsiness was not usually severe but was much more common when the patient had had premedication.

Respiratory system. When injected rapidly, sneezing, coughing and retching occurred. Respirations were slowed and reduced in depth. These returned to normal within two minutes, while operative stimulation increased depth and rate.

Cardiovascular system. The systolic blood pressure drops with little change in the diastolic. Slight bradycardia occurred during induction. These blood pressure changes returned to normal 4–5 minutes after start of injection and the pulse rate within 2 minutes. It is interesting to note that Ruddell (23) mentions "once the blood pressure starts to rise, it appears that the patient is ready for operation."

Central nervous system. The drug was given to a volunteer (22) (600 mg. was injected slowly over a period of 1½ minutes). Drowsiness occurred, followed by rapid loss of consciousness. After a further 1½ minutes, 400 mg. was injected quickly. Painful stimuli then increased the depth and rate of respiration. This could be a sign of its poor analgesic property. The subject regained consciousness after 6 minutes without mental confusion. There was no retrograde amnesia. After a further 6 minutes he was able to walk straight, and within 22 minutes wrote an account of the subjective sensations. Slight euphoria persisted for about 2 hours. Transithal has been used for "narco-relaxation" (24) where tension is a prominent feature. In divided doses and injected slowly it was noted that the patient first felt the effect 1½ minutes after the start of injection, experiencing much relief of tension and a feeling of well-being. There was controlled relaxation without impairment of consciousness and sleep was produced by increasing the rapidity of injection. It was also noted that if the drug was withheld for a minute or two, the patient returned to consciousness. No side actions were noted, neither was excitement seen.

Other effects. There was no alteration in blood volume. The initial blood pressure drop is attributed to a decrease in the blood flow in the relaxed muscles. As in the case of hexobarbitone, there was little effect on the blood sugar. The blood coagulation was unaffected. Evidence from animal experiments suggests that the drug should not be given intramuscularly (21). This drug has also been used in electroconvulsive therapy, when it was found that doses of 250–500 mg. injected over one-half minute caused less depression than thiopental, and that patients speedily returned to consciousness. It was further stated that side actions such as hiccoughs and retching were no more common than with thiopental.

Methitural Sodium (Neraval®): Personal Cases

Following encouraging reports of others, we investigated some of the properties of Neraval (methitural sodium). The intention was to use it mainly for anaesthesia during electroconvulsive therapy, with the purpose of evaluating some of its pharmacologic actions, particularly its relaxant effect, if any. In order to augment our series, it was also used in various minor surgical operations such as incision and drainage, and reduction of fractures and dislocations. No attempt was made to select the type of patient. The majority of patients were between the ages of 60–69 years.

Technique

The patients for electroconvulsive therapy were premedicated with the usual dose of atropine one hour before anaesthesia. No barbiturate or opiate was given with the atropine. A 2.5 per cent solution of Neraval alone was used for all these patients. A higher concentration was not used because of previous reports of others on the incidence of side effects such as spasms, cough and hiccoughs. Oxygen alone was administered during these very short procedures. Cases which were going to last more than ten minutes were given a continuous infusion of 0.6 per cent Sodium Neraval solution supplemented by 50 per cent nitrous oxide and oxygen.

Results

One of the first characteristics of the drug noted was the long lag between start of injection and effect of the drug, so that there was a tendency to give more drug than it was considered the patient actually needed for the procedure. There was a high incidence of laryngospasm and coughing when the drug was injected rapidly, but none occurred when the required quantity of drug was injected over a period of not less than 45 seconds.

Less salivation followed the electroconvulsive therapy under Neraval compared to those cases anaesthetized with sodium amytal alone. This was very significant because most of those patients done under other barbiturates had profuse salivation during and after the shock, with resulting cyanosis and coughing. Such was not the case in the surgical patients, as no marked salivation occurred in those operated on under other barbiturate anaesthesia. The patients maintained a very good colour throughout the procedure. This may well be due to the fact that these patients received 100 per cent oxygen prior to the shock.

Hiccoughs almost always appeared after the shock, lasting on an average five minutes, and disappearing spontaneously.

Apnoea was related to the dose given. At the beginning of the series, when more drug was given than was needed, there was an average apnoea lasting 2 to 3 minutes.

Some relaxation was definitely produced as evidenced by the fact that tonic and clonic contractions were never violent. This gave the impression that some curare-like drug had been given with it.

The recovery period was definitely rapid. Most of the patients were able to answer questions before they were returned to their wards.

More definite observations were made on the surgical patients as there was no other condition with them which might affect the patient, as the electro-shock does.

(1) The respiration was definitely depressed during anaesthesia. In a few patients the depression simulated that of morphine.

(2) Analgesic property was poor.

(3) Systolic blood pressure fell appreciably—about 20–30 mm. Hg, although there was less change in the diastolic blood pressure.

It is not certain whether the above observations were due to over-dosage or not. An attempt was made to use the drug alone, and it is quite probable that it was used to a point of over-dosage which produced the above findings.

The most impressive property of Neraval was the rapid recovery. Patients were awake and coherent within 15–20 minutes.

SUMMARY

An attempt has been made to show the slow progress of intravenous anaesthesia. Some of the newer thiobarbiturates which have been and are being evaluated have been reviewed. A preliminary report of our experience with methitural sodium (Neraval Sodium) is presented. It seems that the only definite advantage it has over those presently used is the rapid recovery. Before one can even predict whether this drug will have a definite place in anaesthesia, it must be subjected to more rigorous studies.

ACKNOWLEDGMENTS

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The methitural sodium (Neraval Sodium) used in this study was supplied through the courtesy of Schering Corporation Limited, Montreal, Quebec.

RÉSUMÉ

Tout en montrant les progrès lents de l'anesthésie intraveineuse, nous avons voulu, au cours de ce travail, faire une brève revue des différents thiobarbituriques et plus spécialement du Néraval qui a été l'objet de recherches récentes.

En effet, il y a environ deux ans, un nouveau barbiturique à action ultra-courte était connu sous le nom de Néraval. Cette nouvelle substance est surtout remarquable parce qu'elle permet un réveil plus rapide qu'avec le pentothal ou le surital.

Le Néraval contient le radical méthylthioéthyl que nous trouvons également dans la méthionine, un acide aminé essentiel important dans le processus de détoxification. Ceci explique son action ultra-courte due à sa destruction rapide et à son élimination par le foie et les reins.

A la suite de rapports encourageants, nous avons décidé d'employer le Néraval comme anesthésique de base au cours des anesthésies pour électrochocthérapie au lieu d'amytal ou de pentothal. Notre intention était de voir s'il donnait ou non un certain relâchement musculaire (curare-like). Nous avons d'abord remarqué que la coloration des patients anesthésiés au Néraval était toujours rosée contrairement à ceux qui recevaient de l'amytal ou du pentothal. Un certain degré de relâchement a été définitivement constaté donnant même l'impression qu'une dose de succinylcholine aurait été donnée en même temps. En effet, les contractions toniques et cloniques ne furent jamais violentes après injection de Néraval.

Le réveil était beaucoup plus rapide qu'avec les autres substances employées, cependant que nous avons noté un temps assez long entre le début de l'injection du Néraval et la perte de conscience.

Nous avons remarqué une diminution nette des sécrétions salivaires après les électrochocs si nous comparons avec des patients anesthésiés à l'amytal.

Cependant, nous avons noté une assez forte proportion de toux et de laryngospasme léger quand le Néraval était injecté rapidement, incident évitable en injectant lentement.

Le Néraval a été employé aussi comme anesthésique de base au cours de diverses autres interventions mineures avec des résultats satisfaisants.

La principale propriété du Néraval est certes de permettre un réveil rapide. Cependant avant de prédire que cette drogue aura une place définie en anesthésie, nous croyons qu'elle devra être soumise encore à de rigoureuses études.

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REFLEX BRADYCARDIA IN OPHTHALMIC AND OROPHARYNGEAL SURGERY*

F. A. WALTON, M.D.†

A RECENT REPORT by Sorenson and Gilmore (1) has shown that during strabismus surgery cardiac irregularities, particularly bradycardia, occur frequently and may proceed to cardiac arrest. Irregularities (electrocardioscope and radial pulse control) occurred in sixteen out of seventeen consecutive cases. In fifteen patients the pulse, which was between 110 and 130, dropped with tension on the eye muscles (especially the medial rectus) to between 40 and 65 with an average of 49.4. Ventricular fibrillation occurred in one patient. The investigation was prompted by a case of cardiac arrest during traction on the medial rectus in a three-year-old child. This responded to rhythmic thumping on the chest. Further tension on the muscle reduced the heart rate to 40 (from 120). The operation was completed successfully with as little tension as possible on the muscle. The anaesthesia used for these patients was ether-oxygen. Premedication was codeine or methadon and atropine or scopolamine. Varying these premedicants had no effect on the arrhythmias, but atropine 1/150 gr. intravenously did control them. Hypoxia was probably not a factor in these cases as oxygen was the vehicle for the ether.

The authors point out that vagal tone reaches its peak during adolescence and early adulthood and that the occulo-cardiac reflex is positive in 90 per cent of children. They cite Aschner (2) who demonstrated by nerve sections in animals that the afferent limb of this reflex is the trigeminal nerve. Lyle (3) is also cited to the effect that all trigeminal nerve divisions carry sympathetic and parasympathetic components. Parasympathetic fibres, especially, are present in the ciliary ganglion and in the ciliary nerves. Reid *et al.* (4) state that a *healthy* heart will never respond to vagal stimulation with serious symptoms, but anaesthesia renders the heart vulnerable to vagal stimulation by depression of the functional capacity of specific fibres in the myocardium.

In 1952 Papper and Howland (5) described bradycardia due to pressure on the eyeball by the head rest during cranial surgery under Pentothal/N_2O anaesthesia. They also describe two cases of reflex cardiac arrest from dural stimulation.

The paper by Sorenson and Gilmore has been extensively quoted and its importance and originality certainly deserve a wide audience. It serves as an introduction to the following observations over the past few years. My interest in this subject was first aroused in 1948 when I was called in to assist in the resuscitation of a girl of seven whose heart had stopped suddenly shortly after surgery had started on the internal rectus muscle of her second eye. Anaesthesia was ether insufflation and had been quite uneventful during the surgery on the first eye. A few drops of adrenaline had been instilled into the conjunctiva incision just prior to the arrest. The heart was not fibrillating, and intracardiac adrenalin,

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artificial respiration with oxygen and cardiac massage for over two hours were unfortunately of no avail. Discussion at this time revealed that some time previously, in another hospital, a child had died suddenly and unexpectedly while the head bandage was being applied at the completion of the operation. This first case was inexplicable at the time, although the adrenalin was naturally under suspicion. The effect of the atropine would be worn off by the time operation on the second eye was started. This was probably the most important factor. The second case could be explained by pressure on the eyeball by the bandages causing bradycardia and ultimately cardiac arrest.

Clinical

It was decided that the heart or the pulse would be monitored constantly in all eye operations, particularly in muscle operations on children. It was quite apparent that clearing or traction of eye muscles in children under ether/N_2O/O_2 (5/2 litres per minute) anaesthesia frequently produces a bradycardia, especially when the internal rectus is being worked on. It was decided, therefore, to give d-tubo-curarine-chloride 1 cc. (3 mg.) or Flaxedil[1] 1 cc. (20 mg.) intramuscularly after induction and intubation, in order to reduce the amount of ether needed and also to relax the eye muscles. Adults and children from age six up were given an intravenous induction that included Demerol, Mecostrin[2] or Flaxedil, and thiopentone followed by intubation and N_2O/O_2:5/2 litres per minute. Of twelve patients undergoing muscle operations (average age 10 years)—three with ether/-N_2O anaesthesia (two with intramuscular relaxant), nine with intravenous anaesthesia—only three showed any bradycardia, and this was not marked. In a nine-year-old boy (intravenous anaesthetic) the pulse slowed from 110 to 88 or 80 on more than one occasion when the internal rectus was being cleared. The bradycardia was self limited. This boy had had his atropine (1/150 gr.) two hours previously instead of the usual 20–40 minutes preoperatively. Another (ether-OT#2-N_2O), a two-year-old boy, had had only 1/250 gr. of atropine and had not been given any curare or Flaxedil. His pulse dropped suddenly from 160 to 128 when pulling on the internal rectus; this was also self limited. The third, a two-and-a-half-year-old girl (ether-N_2O), had been given Demerol 15 mg. and Flaxedil 10 mg. intramuscularly, before starting the first eye. The pulse *rose* when clearing the medial rectus. Ether was used when the second eye was being done (during the second hour) and a bradycardia 160 → 120 occurred when traction was applied to the medial rectus. A man, age 27, who had morphine gr. ¼ and scopolamine 1/150 gr. preoperatively and a Demerol-Mecostrin-Pentothal-N_2O anaesthetic had a *transient* bradycardia—from 60 to 50 with a blood pressure drop from 135 to 110 systolic each time each eye was pulled down forcibly to expose the superior rectus and superior oblique muscles. Other eye operations on adults, enucleation 7, cataract removal 1, iridectomy 4, showed no bradycardia or drop in blood pressure. In fact, the blood pressure rose 15 mm. Hg. in two patients as the snare freed the eyeball and in another patient the pulse rate *rose* from 72 to 100 and the blood pressure rose 20 points when the internal rectus was being cleared. These patients all had intravenous anaesthesia including *Demerol* (preoperatively also), Mecostrin or Flaxedil and Pentothal/N_2O.

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[1] Gallamine tri-ethodide.

[2] d-tubo curarine dimethyl ether chloride.

More recently other causes of bradycardia in children have been noted. An extremely agitated girl of nine had to have an emergency oesophagoscopy. She was given atropine 1/150 gr. intramuscularly about 15 minutes preoperatively. The anaesthesia was Vinethene[3] ether followed by endrotracheal N_2O/O_2 5/2 litres per minute. She became pulseless on three occasions when the oesophagoscope was opposite the heart. This condition was relieved each time by withdrawing the scope. A similar situation occurred with a two-year-old boy having an oesophagoscopy. A five-year-old boy who had had *rheumatic fever* and had a heart murmur was having a tonsillectomy and adenoidectomy. The anaesthesia was Demerol 50 mg. Mecostrin 2½ mg.-Pentothal 2 per cent 6 cc.-oxygen-#3 orothracheal tube-N_2O 5/2 litres per minute. His pulse slowed suddenly from 160 to 88 on three occasions while the adenoids and adenoid fossa were being dealt with. Reid (4) describes a patient who similarly developed cardiac arrest each time the adenoid fossa was stimulated. The reflex was controlled ultimately by intravenous atropine. A girl of eight years who suffered from *asthma* and still had some rhonchi was given a Vinamar[4]-ether-orothracheal tube #3-N_2O anaesthetic. While a tonsil was being guillotined the pulse fell temporarily from 135–140 to approximately 80. A girl of 15 months was given a Vinamar–ether–orotracheal tube #1–N_2O anaesthetic. Her pulse dropped suddenly from 160 to 115 when the doctor was pulling on the left tonsil. She had only had 1/300 gr. of atropine and was "wet" as well. A relatively mild bradycardia has been noticed in two other patients undergoing tonsillectomies–one (aged 4) under ether; one under intravenous anaesthetic–and may have been present on other occasions as assisting at the operation does not allow one to monitor the pulse constantly. However, the boy who had had rheumatic fever probably had some cardiac damage and the girl with the asthma might well have had a vagal predominance. The third little girl was not well atropinized and had an ether anaesthetic. For several years now, we have been giving anaesthesia for dental fillings and extractions. The average age of these patients is five years. Generally speaking those five years or over are given an intravenous anaesthetic of Demerol-Mecostrin or Flaxedil-Pentothal-O_2-intubation-N_2O, while the younger ones received a Vinethene or Vinamar ether induction followed by intubation and N_2O with ether when needed. It was noted that the latter group often developed a bradycardia, for example, from 130 to 50 when drilling steadily without a pause. This bradycardia was easily terminated by stopping drilling for a few seconds. Bradycardia *did not occur* when an intravenous anaesthetic as above was used; in fact, in some patients the pulse rate rose with persistent drilling, a pain effect. Latterly some smaller patients have been induced with rectal Pentothal (about 10 cc. of 2 per cent) and about twenty minutes later given Demerol (35–50 mg.) and Mecostrin

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[3] Di-vinyl ether.

[4] Ethyl vinyl ether.

(1½–2 mg.) intramuscularly. About fifteen minutes later they are given Vinamar or ether inhalation, intubated and carried on N_2O/O_2 5/2 litres per minute. In these cases also no bradycardia occurs. Some of my colleagues use N_2O and trilene after intubation and state that bradycardia does not occur, presumably because they use no more ether.

Discussion

A large experience with Demerol-Mecostrin-N_2O anaesthesia (6) indicates that the pulse is remarkably regular in rate and rhythm and is often around 60 to 70 per minute in adults and averages about 135 in children (age 2–6 years). Cardiac irregularity is *very unusual* and vagal depression of the pulse rate or blood pressure has only occurred in one case, to my knowledge, exclusive of the above cases. This was due to direct pressure with a retractor on the pericardium and ceased when the pressure was released. On the other hand, it would appear that *ether* sensitizes the heart to vagal effects, probably by a selective myocardial depression. The same effect may occur without ether if there is previous myocardial disease and/or a marked vagotonia. Atropine also, in insufficient or too early dosage, may allow a vagal effect to show. The mild vagal effects in the three Demerol-Mecostrin-N_2O anaesthetics mentioned above have not been noted in any case where Flaxedil was the relaxant used. Flaxedil has a vagolytic effect and the pulse is ten beats faster per minute on the average (7). Average pulse rates in children age 2–6 undergoing various operations are: Demerol-Flaxedil-N_2O anaesthesia, 145; Demerol-Mecostrin-N_2O, 135; N_2O-ether, 154. The increased pulse rate may be due to the increase in metabolism with ether whereas the non-volatile anaesthetics, especially Demerol, depress the metabolism.

Conclusions

Reflex bradycardia and, occasionally, cardiac arrest may occur during eye muscle operations. This is much more common under ether anaethesia. Bradycardia may also occur during other procedures involving the mouth, pharynx or oesophagus. Cardiac or pulmonary disease may predispose the patient. These effects may be mitigated by adequate timely atropinization,[5] and less reliance on ether as the sole anaesthetic. Mecostrin or Flaxedil intravenously or intramuscularly will reduce the incidence and severity of bradycardia also. Morphine or other opium derivatives might well be avoided on account of their vagomimetic action. Demerol has some vagolytic action and is therefore protective. The bradycardias may be terminated by ceasing the stimulation producing them or by intravenous atropine.

During eye operations, at least, the pulse or heart must be constantly monitored. It appears that this may also be advisable when drilling teeth under anaesthesia.

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[5] Hypodermic atropine reaches its peak effect in 20 minutes and is practically inactive at 90 minutes. In practice, giving the child atropine just before leaving the ward for the operating room is very satisfactory: i.e., "on call" or "on the stretcher." Earlier administration plus some delay in starting the anaesthetic results in poor atropinization.

It is probably wise to have a *slow* intravenous running also so that atropine may be given intravenously when needed.

Although my experience is limited, I understand that bronchoscopy under general anaesthesia is considered to be a dangerous procedure in small children. On theoretical grounds this is certainly not surprising. Ether anaesthesia, possibly hypoxia, and vago-vagal reflexes all being combined in many cases. I know of one case of severe bradycardia in a child of seven who was having a vaginal examination that necessitated some forceful dilation. The anaesthesia was ether-N_2O.

Finally, I feel reasonably certain that hypoxia and/or hypercardia were not the factors in the cases presented here. All the patients received nitrous oxide oxygen 5/2 litres per minute and respirations were assisted or controlled when necessary.

SUMMARY

Attention is drawn to the rather common occurrence of bradycardia in children undergoing eye or oro-pharyngeal surgery. This incidence is increased by inadequate atropinization, too much reliance on ether as the main anaesthetic agent, and cardiac or pulmonary disease. Demerol, Flaxedil or Mecostrin have a protective action in this respect.

RÉSUMÉ

Nous attirons l'attention sur l'observation assez fréquente d'une bradycardie chez les enfants soumis à la chirurgie ophtalmique ou oropharyngée. Cette bradycardie peut précéder l'arrêt cardiaque. Cette observation est plus fréquente si l'atropinisation est insuffisante, si l'on compte trop sur l'agent anesthésique principal et dans les cas de maladies cardiaques ou pulmonaires. Le Demerol, le Flaxedil ou Mécostrin peuvent exercer une protection dans ces cironstances.

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ANAESTHETIC EXPERIENCES USING EXTRACORPOREAL CIRCULATION FOR OPEN HEART SURGERY*

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AS A RESULT of the rapid advances in cardiac diagnosis in recent years, most centres have established diagnostic cardiovascular units. These units have diagnosed a large number of remedial congenital lesions and consequently trained cardiovascular surgeons have been attracted to these centres. Initially, they operated only on those lesions which could be remedied without stopping or opening the heart, and which did not require a bloodless field. Most of these procedures were blind procedures and the result often left much to be desired. The demonstration of the feasibility of operating in a bloodless field using hypothermia was a major advance. Hypothermia, however, carries its own hazards; the main drawbacks were the severe time restriction placed on the surgeon and, when operating upon ventricular lesions, the ever-present possibility of ventricular fibrillation.

PUMP OXYGENATOR

In recent years a few centres have reported an increasing number of successes using the low-flow bubble oxygenator pump for open-heart direct-vision surgery (1,2). Many modifications of this pump oxygenator have been developed, but mostly in the oxygenator, and these so-called low-flow systems are now in use in many centres. This indicates that anaesthetists must shortly become familiar with this technique.

The low-flow pump oxygenator was developed (1) on the basis of the principle of azygos-flow which had proved that flows of 8–14 cc. kg./min. would keep dogs alive. This principle allowed the development of this simple low-flow machine. With the low-flow there is less coronary bleeding during cardiotomy; therefore, there is less blood loss and less blood is required to prime the pump.

With the original flow rates of 35–40 cc. kg./min. in humans there was little evidence of cardiac hyper-irritability. Most workers are now using higher flows ranging from 60–100 cc. kg./min. The newer pumps will deliver up to 3 litres/min. as compared to a previous 2 litre/min.

This bubble oxygenator provides a normal oxygen saturation. Since it is an open system, the blood leaving the pump has lost a great deal of its CO_2 and has a PCO_2 of 20–30 mm. Hg because the CO_2 is blown off by the oxygen stream in the oxygenator. Some believe that this should be prevented and so use a CO_2–O_2 mixture in the oxygenator. We prefer the respiratory alkalosis which results. We have not encountered any of the deleterious effects which Mendelsohn (2) attributes to carbon dioxide washout.

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During the perfusion the mean brachial artery pressure is about 50–60 mm. Hg. There is occasionally a rise in venous pressure which is usually the result of mechanical obstruction from the use of caval catheters which are too small. Some (2) prefer to give vasopressors to raise the arterial pressure during the perfusion. We have not attempted this. With the flows now used there appears to be adequate cerebral perfusion as shown by the lack of any change in the postoperative electroencephalographic pattern or in the postoperative clinical condition of the patient. This pump oxygenator is not the ideal desired as the blood flows and arterial pressures are far below normal, and considerable trauma to the blood occurs; this results in considerable metabolic change.

ANAESTHESIA

The anaesthetist who is familiar with the anaesthetic problems of today's routine cardiac surgery will not find any particular anaesthetic problem with these cases. The same principles must be adhered to: exceedingly light levels of anaesthesia; perfect controlled ventilation (which is often difficult to achieve because of a large heart, bilateral pneumothorax, and frequent surgical retraction of the lungs); and adequate but never excessive blood replacement. This latter is essential and is one of the most trying problems.

Anaesthesia has been induced by thiopentone with succinylcholine, or cyclopropane oxygen with succinylcholine, followed by endotracheal intubation and controlled respiration using a circle absorber with high gas flows. It has been maintained either with nitrous oxide–oxygen 60:40 with intermittent succinylcholine, or with ether-oxygen analgesia. The latter is preferred by many of us. We prefer to avoid intravenous agents as much as is possible in these patients. The anaesthetic agent chosen is not of great importance as long as it is used correctly. The only respiratory complications which occurred were in four patients anaesthetized with nitrous oxide-oxygen and succinylcholine. Two of these patients had exceedingly high right ventricular pressures and this type of case is prone to develop respiratory complications (1,2). We cannot agree with Mendelsohn's (2) opinion that ether causes a greater incidence of respiratory complications; as yet we have not encountered any with ether.

During by-pass gaseous agents are eliminated and the patient awakens; if the patient does not awaken then, we are concerned. It is often necessary to give a very small dose of barbiturate or meperidine and succinylcholine to control the patient during by-pass. We have not attempted to anaesthetize the oxygenator (2,4) and as this is such an open system we doubt if it would be effective unless very high concentrations of anaesthetic gases were used. This we consider to be too dangerous when this open system and a pump which is not explosion proof are used.

This problem of awakening rarely occurred when flows of 35–40 cc. kg./min. were used as the cerebral hypoxia was usually sufficient anaesthesia. Now, with flows of 60 cc. kg./min., the patient invariably awakens and commences to move.

Only minute doses of barbiturate or meperidine are required in most instances in spite of the high dilution of the drug by the patient's blood plus the blood in the pump.

The electroencephalograph is used constantly and is believed to be one of our most valuable monitors (3,4). It tells us the depth of anaesthesia, the state of the cerebral circulation and the operating efficiency of the extracorporeal circulation. If there is deep anaesthesia, obstruction to the arterial or venous flows, or a shunt as with an unrecognized patent ductus, the electroencephalograph will immediately give a gross easily recognized warning. An occasional complication, which the anaesthetist must watch for, is cerebral congestion; it is usually the result of mechanical obstruction and is readily detected if the electroencephalographic record and the congested appearance of the head are noted. Other monitors which help the anaesthetist are the electrocardiograph and the intra-arterial and intravenous pressure tracings. The latter are of considerable help as an aid in regulating blood replacement.

During the extracorporeal circulation no anaesthetic gases other than oxygen are given. The lungs are maintained partially inflated to prevent complete collapse, but respiratory exchange is not necessary during this period.

Blood loss is often considerable when the heart is opened. No serious attempt is made by the anaesthetist to replace this loss, which can be done much more efficiently by the pump. Before by-pass is commenced blood loss is replaced as accurately as is possible by the anaesthetist, using citrated blood. When by-pass and cardiotomy and repair are commenced, two suction set-ups, one for the heart and one for the chest cavity, are used, all blood lost is suctioned and measured in sterile calibrated containers. The blood from the heart suction is returned to a special pump and can be recirculated if necessary. The fall in blood level of the pump helix approximates closely the blood lost through the suctions. This is replaced by adding blood to the pump and all replacement is carried out by the pump until the catheters are removed when the anaesthetist again assumes this duty.

The patient is weighed before and after surgery as a check on blood replacement, and recently radioactive chromium estimations are being done when possible. It is believed that, if heart action is good, the intra-arterial and intravenous pressures, plus the anaesthetist's estimate of the patient's condition, are the best indicators of the adequacy of blood volume regardless of measured loss and replacement.

The use of cardiac arrest greatly reduces the blood loss since there is no coronary flow. Cardiac arrest produced by acetylcholine was used routinely for a few patients, but the surgical team did not feel that the advantages outweighed the possible risks, especially during long perfusions; the surgeon's difficulties created by a moving heart have decreased with experience and cardiac arrest is seldom used now. It is not known how long the arrested heart without coronary circulation can survive without damage to myocardium and conductive tissue. At present cardiac arrest is only produced when the surgeon believes that it is necessary for technical reasons.

Surgical Procedure

Briefly the surgical procedure is as follows. The inferior and superior venae cavae are catheterized through the right atrial appendage for the pump inflow, and the femoral artery is catheterized for the pump outflow. The patient is previously heparinized with heparin 1.5 mg./kg. The base of the aorta is cleared and an exploration for a patent ductus is made routinely.

During this period the pump is being primed with heparinized blood which is collected the same morning and the pump is calibrated for the desired output. Following exploration for the ductus the pump is started and run for about thirty seconds before the venae cavae are occluded; then continued for another one or two minutes after total venous occlusion. If the electroencephalograph is satisfactory, the pupils remain constricted and there is no evidence of venous congestion, the aorta is clamped and acetylcholine 10 mg./kg. is injected into the base of the aorta to perfuse the coronaries (this only if cardiac arrest is desired), when cardiac arrest occurs rapidly.

Cardiotomy is then performed and the repair carried out. Following repair and closure of the cardiotomy the clamps are removed from the aorta and venae cavae and perfusion of the heart occurs, if cardiac arrest has been used, the acetylcholine effect disappears, and a normal beat is resumed in a matter of 1–2 minutes. The pumps are then stopped and the anaesthetist surveys the patient's clinical condition and estimates the need of further transfusion. If he believes that further blood replacement is required, he orders what volume he wishes to be given from the pump. This is done by turning on the outflow side of the pump only and may be repeated several times until the anaesthetist is satisfied. With the heart and the intra-arterial and intravenous pressures under constant observation, overload is easily detected and if it should occur the excess blood can be removed by utilizing the venous side of the pump; we prefer to be slightly deficient in blood replacement.

When everybody concerned is satisfied with the clinical state of the patient the catheters are removed, protamine 1.5 mg./kg. is given and the closure commences. The anaesthetist changes back to citrated blood and this is used until all evidence of blood loss ceases. This period may last 48 hours as every drop from the chest drains in the postoperative period is accurately measured and usually replaced.

The patient should be awake before leaving the operating room, preferably before the last sutures are inserted. If the patient is not awake then cerebral hypoxia has probably occurred either from poor perfusion or possibly from air embolism. Anaesthetic overdose should not occur with the technique used. One can usually predict from the EEG. during and after the perfusion whether there will or will not be a delay in recovery. In three patients return of consciousness was delayed for 30–60 minutes. Early in this series one patient suffered severe cerebral hypoxia and did not awaken for 48 hours, then made a rapid and apparently uncomplicated recovery; air embolism was suspected as the EEG. pattern deteriorated after the aortic clamp was released.

During and after operation arterial blood samples are taken frequently for study. The physiological changes which occur have been presented in detail by others (1,2,3) with much larger series. Here, it suffices to say that biochemical changes are infrequent until after the termination of the by-pass. At this time significant metabolic acidosis often begins to manifest itself, especially with very long perfusions and in cyanotic patients, but rarely after short runs of ten to fifteen minutes. The acidosis is the result of an increase in lactic acid with a fall in bicarbonate, most likely the result of the low tissue perfusion. If severe this acidosis is treated with intravenous bicarbonate. If circulation and respiration are adequate after by-pass, the acidosis will correct itself in most patients. Hypokalemia usually occurs in acyanotic patients, but a hyperkalemia may occur in those who are cyanotic. The potassium disturbances are rarely severe enough to require treatment. There is a marked rise in blood sugar levels, but other biochemical changes have not been significant.

Haemolysis occurs in every case. The amount is usually directly proportional to the flow and duration of the pump run. As yet no ill effects have been noted from haemolysis; levels under 200 mg. per cent appear to be innocuous (1). Very little is known of other changes in the blood factors other than that severe platelet destruction occurs. Bleeding and clotting times have all been normal after protamine. Some writers have emphasized the difficulty with post-operative bleeding (1,4), It occurred in two patients in this group; one required operative correction. One patient developed an uncontrollable haemorrhagic diathesis during surgery; citrate intoxication was suspected.

Arrhythmias after repair of the defect have been a frequent problem. One patient with supraventricular tachycardia was effectively treated with methoxamine. Four patients (one with Eisenmenger's Complex, two with Tetralogy of Fallot, one with an atrial-septal defect) developed an A.V. conduction defect. All except the one with the atrial-septal defect died suddenly, 9, 24, and 2 hours postoperatively. All had apparently recovered and were maintaining an adequate circulation, when presumably complete block developed. Sudden, unexpected, unexplained death in the first 24 hours is not a rarity. This has been the experience of all workers in this field and it has been suggested that post-operative oedema from the repair interferes with the conductive tissue of the heart causing sudden cardiac standstill. Conduction defects are frequent with some ventricular septal defects and with atrial ostium primum defects. Isopropylarterenol has been used for the treatment of these conduction defects, but with little success in our cases.

There has not been any clinical evidence postoperatively of any damage to vital organs attributable to the pump oxygenator. None of the deaths could be attributed to the pump or anaesthetic agent or method of administration.

Table I shows the perfusion and anaesthetic times and some of the more important biochemical changes. More extensive details of this nature are to be found in Buckley's (1), Mendelsohn's (2) and Matthew's (3) papers.

The following tables show that a wide variety of lesions have been treated. No attempt was made to select the patients; all were treated as they were brought to the cardiovascular unit. Many patients had multiple cardiac defects and all

TABLE I

Patient	Age	Sex	Weight (kg.)	Diagnosis	Run (min.)	Anaesthetic time (hr.)	Cardiac arrest	Post-run art. pH	Post-op. (km./Eq.)	Hemolysis (mg.%)	Flow rate (c.c./kg.)	Anaesthetic agent
1	32	M	70	Pulmonary stenosis	6	7	No	7.46	3.9	32.6	30	N_2O, O_2 P.†F.‡
2*	40	F	45	Mitral stenosis and aortic regurgitation and tricuspid stenosis	10	5	No	7.44	—	75	35	N_2O, O_2 Succ.*
3*	2½	M	11	I.A.S.D.—Ostium: Primum	24	6	No	7.27	6.7	78	35	N_2O, O_2 P.F.
4	10	F	28	I.A.S.D.	9	4½	No	7.30	3.9	25	35	N_2O, O_2 P.F.
5*	7	M	20	I.V.S.D. and corrected transposition	4	4	No	7.38	6.3	44.5	35	N_2O, O_2 P.F.
6*	6	M	17	I.V.S.D. and pulmonary stenosis	15	5¾	Yes	7.21	4.3	66	40	N_2O, O_2 Succ.
7	9	M	30	Pulmonary stenosis	4	5	No	7.35	3.3	—	35	N_2O, O_2 Succ.
8	1½	F	11	Tetralogy of Fallot	32	5½	Yes	7.37	4.8	46	40	N_2O, O_2 Succ.
9*	5	M	12	Eisenmenger's Disease	39	5	Yes	7.23	2.6	118	40	Ether–O_2
10	12	M	36	I.A.S.D.	17	5¼	No	7.32	3.8	44	35	N_2O, O_2 Succ.
11	7	F	17	I.V.S.D.	29	4½	Yes	7.39	3.4	80.4	50	N_2O, O_2 Succ.
12	9	F	20	I.V.S.D.	27	5	Yes	7.41	3.75	60	50	N_2O, O_2 Succ.
13*	22 mo.	M	12	Tetralogy of Fallot	51	4¾	Yes	7.21	3.8	66	60	Ether–O_2
14*	1½	M	11	Tetralogy of Fallot	32	5¼	Yes	7.17	4.3	124	50	N_2O, O_2 Succ.
15	4	M	14	I.A.S.D.	17	4¼	No	7.31	3.5	70	60	N_2O, O_2 Succ.
16*	14 mo.	M	8	Pulmonary stenosis and tricuspid stenosis and regurgitation	101	7¼	No	7.17	3.1	177	70	N_2O, O_2 Succ.
17	28	M	57	Pulmonary stenosis	4	4½	No	7.41	4.25	7	35	N_2O, O_2 P-Succ.
18	3	F	12	Tetralogy of Fallot	58	5	No	7.29	4.8	161	60	Ether–O_2
19	14	F	38	Trilogy of Fallot	59	6	No	7.14	3.4	86	50	N_2O, O_2 P-Succ.
20	6	F	14	I.V.S.D.	19	5	No	7.35	—	92	60	Ether–O_2
21*	6	M	19	I.A.S.D. and I.V.S.D. and Anomalous drainage	34	6	No	7.29	2.4	123	50	Ether–O_2
22*	5	F	14	Tetralogy of Fallot	62	6¾	No	—	—	—	65	Ether–O_2
23*	9	F	17	I.V.S.D. and Transposition	174	9	No	7.08	—	313	60	Ether–O_2
24	7	M	28	Pulmonary stenosis	10	4½	No	7.31	3.6	—	50	Ether–O_2
25	35	F	54	I.A.S.D.	24	4½	No	7.25	3.9	106	40	Ether–O_2

*Deaths †P–Pentothal (Thiopental) ‡F–Flaxedil (Gallamine) **Succ.–Succinylcholine defects were repaired except one (case #5). Four patients had undergone previous palliative cardiac surgery with poor results; none survived this procedure. The over-all mortality was 44 per cent. For twelve patients with single defects the mortality was 8.3 per cent.

The fatalities are listed below.

Lesion	*Number of each*	*Deaths*
Interventricular septal defect	3	0
Interatrial septal defects:		
Ostium primum	1	1
Ostium secundum	4	0
Pulmonary stenosis	4	0
Trilogy of Fallot	1	0
Tetralogy of Fallot	5	3 (1*)
Interventricular septal defect with pulmonary stenosis	1	1
Pulmonary stenosis with tricuspid stenosis and regurgitation	1	1*
Interatrial septal defect with interventricular septal defect and anomalous drainage	1	1
Eisenmenger's complex	1	1
Transportation and interventricular septal defect	2	2 (1*)
Mitral stenosis with regurgitation and tricuspid stenosis and aortic regurgitation	1	1*
	25	11

Mortality—44 per cent

*Indicates previous cardiac surgery.

It will be seen that most of these were patients with multiple lesions and those patients who had undergone previous unsuccessful surgery using other methods.

We believe that this method for open-heart surgery will soon become as commonplace as pulmonary and neurosurgery, and it is necessary that anaesthetists familiarize themselves with the physiology of these cardiac lesions, with the surgical procedures involved, with the anaesthetic problems which occur, and with the constant changes and advances in this branch of surgery.

Patient	*Lesion*	*Comment*
2	Mitral regurgitation and stenosis	Previous commissurotomy. Cardiac cripple. Severe haemorrhage, died in operating room. Autopsy revealed aortic regurgitation and tricuspid stenosis also present.
3	Atrial septal defect, ostium primum type	Died four hours postoperatively. Severe acidosis, hypotension, hypovolemia. Autopsy negative, Bundle of H is possibly involved in repair.
5	Common ventricle (large I.V.S.D.) and corrected transposition.	Exploratory cardiotomy only. Died twelve hours postoperatively. Clinical cardiac failure. Autopsy negative.
6	Interventricular septal defect and pulmonary stenosis	Suspect air embolus. Coma two days. Good recovery. Wound disruption eighth day and cor pulmonale developed. Cardiac failure during closure. Autopsy: incomplete closure of defect.
9	Eisenmenger's Complex	Post repair conduction defect. Sudden death nine hours postoperatively. Autopsy negative.
13	Tetralogy of Fallot	Post repair conduction defect. Sudden death twenty-four hours after operation. Autopsy: sutures pulled out of septal defect. Outflow patch incorrectly placed.

Patient	*Lesion*	*Comment*
14	Tetralogy of Fallot	Post repair conduction defect. Sudden death two hours postoperatively. Autopsy negative.
16	Pulmonary stenosis with tricuspid stenosis and regurgitation	Previous repair pulmonary stenosis at six months under hypothermia. Died in operating room. Severe haemorrhage during attempted insertion of plastic tricuspil valve. Pulmonary stenosis corrected.
21	Interatrial septal defect with interventricular septal defect and anomalous drainage	Preoperative history of epilepsy. Well for 32 hours postoperatively, then had two seizures and died. Autopsy negative, except one suture pulled out of ventricular septal patch.
22	Tetralogy of Fallot	Previous Brock Procedure. Uncontrollable haemorrhage from tears in left lung. Died in operating room. Autopsy negative, good repair.
23	Interventricular septal defect and transposition	Previous Pott's procedure. Developed haemorrhagic diathesis before by-pass, suspected citrate intoxication. Put on pump and baffle insertion attempted. Died in operating room. Autopsy negative.

Résumé

Nous avons fait part de notre expérience en anesthésie acquise au cours de 25 cas où l'on a employé la pompe de Lillehe et Dewall, oxygénateur barboteur à faible débit. Au cours de ce travail un des problèmes les plus difficiles à été l'évaluation de pertes sanguines et de leur remplacement pour maintenir l'équilibre de la masse sanguine circulante.

L'auteur est d'avis que d'ici à ce que nous ayons acquis plus d'expérience, il est essentiel que, dans ces cas, nous enrégistrions les pressions veineuse et artérielle de même que l'électroencéphalogramme afin d'être renseignés à tous les instants sur les pertes sanguines et leur remplacement, sur le niveau d'anesthésie et sur l'efficacité de la circulation artificielle.

Comme techniques et agents anesthésiques, nous avons employé les barbituriques intraveineux et les paralysants musculaires avec le protoxide d'azote et l'oxygène ou l'analgésie à l'éther. Nous préférons cette dernière technique. Quand nous le pouvons, nous laissons de coté les barbituriques intraveineux qui diminuent le débit cardiaque et s'éliminent difficilement et lentement. En anesthésie, toutes les méthodes sont bonnes si l'on respecte les principes essentiels: une anesthésie très légère et un contrôle parfait de la ventilation. Dans quelques cas, nous avons provoqué l'arrêt cardiaque avec de l'acetylcholine: cette façon d'agir ne présente pas d'avantages et nous l'employons seulement quand le chirurgien l'exige pour certaines raisons techniques.

Il est apparu fréquemment des troubles de conduction, signature d'un pronostic sombre. Il n'a pas été rare de constater des morts subites durant les 24 premières heures. Selon toute apparence, les organes vitaux n'ont subi aucun dommage ni par l'anesthésie ni par la circulation extracorporelle.

Nous n'avons pas tenté de choisir les cas, nous en avions une grande variété: on trouvera dans les tables, les résultats obtenus et les causes de mort. L'auteur

a l'impression que cette technique va devenir bientôt d'usage courant dans les centres importants et que les anesthésistes devraient se familiariser avec les problèmes anesthésiques et chirurgicaux que pose cette section de la chirurgie.

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THE MEDICO-LEGAL RESPONSIBILITIES OF THE ANAESTHETIST*

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CANADIAN ANAESTHETISTS will always record 1942 as a year to remember in the annals of Canadian anaesthesia. During that year Griffiths and Johnson reported their observations on the first use of curare in general anaesthesia. The introduction of curare has been cited by many, as the greatest advance in anaesthesia in the past twenty-five years.

How many of us realize that in that same year there occurred, in the Province of Ontario, another significant event which was to have a momentous bearing on the practice of anaesthesia in Canada? The case of *Hughston* v. *Jost*(1) in that year was the first time in any court in Canada that an anaesthetist had been sued alone for alleged malpractice. From a legal point of view, anaesthesia came of age.

Prior to 1942, the surgeon was considered to have full charge of the operating room, including the anaesthesia and the anaesthetist. The surgeon was held responsible for any ill result from the anaesthetic, although the physician administering the anaesthetic could be held co-responsible.

In the Hughston and Jost case referred to above, the anaesthetist alone was sued for alleged ill result following intravenous Pentothal anaesthesia. The surgeon appeared as a witness, but was not involved in the action. Anaesthesia had become a speciality, and the anaesthetist a specialist.

In Great Britain, the United States, and Canada, anaesthetists in recent years have been subjected to many threats, writs, court actions, judgments and settlements.

The purpose of this paper is to draw attention to observations that might be helpful in the prevention of such threats, writs and court actions.

Let us remember that, as anaesthetists, we are physicians, and any physician may be sued. No one can prevent a patient from bringing action against us, justified or not.

What precautions must we take? I shall stress only a few.

Personal Contact with Patient: History and Physical Examination

On agreeing to administer an anaesthetic the anaesthetist accepts a fairly heavy responsibility. Modern anaesthesia carries many patients to the brink of death. It is therefore essential that the anaesthetist should be cognizant of the patient's medical history and most certainly his physical condition.

This implies personal contact between anaesthetist and patient. Personal contact will help to build up confidence in the patient, and a patient who trusts a physician is less likely to lay a complaint. Many patients have refused to pay accounts on the premise that: (*a*) they had no contact with this phantom

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individual, the anaesthetist, and (*b*) that a contract was not made with this nebulous character to administer an anaesthetic to him.

All of us realize that knowledge of allergy to drugs and anaesthetic agents, previous spinal headaches, previous backaches, previous unfortunate experiences with anaethesia, etc., is essential to the proper selection of anaesthetic agents and techniques; and certainly we all know that specific medical conditions contraindicate the use of certain agents and techniques.

As practising physician anaesthetists, we should contact the patient personally and obtain the above knowledge, and, most important, pertinent medical history and physical examination should be recorded on the hospital chart previous to administration of an anaesthetic. Numerous writs have been issued for alleged damage to teeth—in what condition were those teeth prior to the administration of the anaesthetic? Our group was recently served with a writ for alleged hoarseness following intubation. The suit was dropped when the fact was established that the patient had been hoarse long before she received the anaesthetic.

These are just a few examples of how important it is to "know your patient" before you administer the anaesthetic.

Consent for Anaesthesia and Surgery

Consent for anaesthesia and surgery, signed by the patient while in his normal state of mind, should always be obtained before administering the anaesthetic. Otherwise, the anaesthetist could be liable for assault. "While in his normal state of mind" is essential. Consent while under premedication should never be accepted. Premedication produces amnesia. If the patient is under legal age, a parent or guardian's signature *must* be obtained.

In our hospital the policy is never to administer an anaesthetic until the consent form is signed. If the patient cannot sign because of his condition, we insist that an immediate relative give written consent or the surgeon sign an affidavit stating that the operation is an absolute necessity. For "staff," or "charity" patients a hospital administrator signs. You have read in the newspapers, many times, how patients have sued doctors for administering anaesthetics and performing operations without consent.

Identification of Patient

We have all heard of the wrong patient being operated upon, or the wrong leg being amputated, or the good eye enucleated. Judgments amounting to thousands of dollars have been rendered against doctors here in Canada for these and similar acts of carelessness. It is as much the anaesthetist's responsibility as it is that of the surgeon to ensure that the correct patient is in fact being operated upon, or that the correct part of the right patient is in fact being operated upon. Check the chart and make sure that you have the right patient—patients with identical names have come to the operating suite from the same ward, with entirely different surgical conditions.

Have the surgeon identify the patient, and under no circumstances start an anaesthetic before the surgeon is known to be available. I know of an incident where an anaesthetic had been administered for an hour when the surgeon was found to be operating in another hospital at the same time. What recourse would that anaesthetist have had if an "accident" had occurred during that anaesthetic?

Administration of the Anaesthetic

Precaution should be taken in administering an anaesthetic to patients with a known "full-stomach." More properly, one should state that an anaesthetic should never be administered to such a patient. Statistics have proven that the greatest percentage of "anaesthetic deaths" are due to aspiration of stomach contents. A street brawl in a large city sent a man to hospital with a fractured jaw. The patient's stomach was known to be full of food and spirits. Operation was not urgent, but was booked as an emergency. The anaesthetic was administered, the patient aspirated and died. The assailant was then charged with manslaughter, not assault, and a writ was issued against the anaesthetist also, for abetting manslaughter.

It is not feasible to have all stomachs empty, especially in maternity cases. But it is possible to delay most operations 4 to 5 hours, or to have the stomach aspirated, and to have a stomach tube inserted.

Our equipment should be in proper working order, and I would especially stress the anaesthetic machine. Soda lime burns of the face due to defective to-and-fro canisters have occurred; ether traps, improperly placed, have produced severe cases of pulmonary oedema; gas cylinders have been placed on the wrong outlets, and several deaths have resulted. Are your machines pin-indexed? Are you using the accepted colour codes for anaesthetic gas tanks?

Syringes, spinal sets, regional block sets should be sterilized by autoclaving. Ampoules ,especially those containing local anaesthetic solutions, should never be soaked in alcohol or formalin, or an antiseptic solution. You are familiar with the famous legal case in England three years ago, relating to spinal anaesthesia, in which the judgment implied that hereafter the use of ampoules sterilized in solutions would be tantamount to malpractice. Also, ensure that the drugs you use come from reputable pharmaceutical firms.

Place a blood pressure cuff on the arm, record the preoperative blood pressure and pulse, and operative blood pressure and pulse. An "anaesthetic death" occurred in the operating room; the anaesthetist's spymanometer was broken and blood pressure was never recorded. The anaesthetist's protective insurance company paid damages without attempting to contest the action.

Before starting a general anaesthetic, have the patient strapped on the table. Several hospitals and personnel have been sued over broken bones occurring from a fall from the operating table. Make sure that an orderly or nurse is present, especially the latter with female patients, for reasons I need not stress here.

Check the patient's posture. Pressure exerted over vulnerable nerves—ulnar, popliteal, brachial plexus, etc.—can and have produced serious neurological sequelae with resultant legal action. To play safe, have the hospital personnel posture the patient, and then you will not be held responsible if any untoward complication appears.

Amputations of legs and arms as a consequence of neglected tourniquets have occurred. If the anaesthetist aids in the adjustment of the tourniquet, he must also accept the responsibility of removing that tourniquet when the operation is completed.

Anaesthetic Mishaps

So called "anaesthetic mishaps" have produced the largest number of threats, writs, and court judgments. Time will not permit me to discuss these but I would like to mention a few.

Orbital area. Corneal abrasions from volatile anaesthetic agents, or corneal abrasions from trauma during or following an anaesthetic have led to a number of serious threats. Conjunctivitis and blindness due to pressure on the eye; or supra-orbital neuritis due to pressure have been known to occur. Do you take proper precautions in protecting the orbital region?

Teeth. Broken teeth, bridges, traumatic removal of teeth, especially in children, have led to the greatest number of threats. Are you protecting the teeth during intubation? If teeth are broken and parts cannot be found, do you X-ray the chest for the missing part? Broken teeth are an accepted hazard in modern anaesthesia, and you must never accept financial responsibility for their repair.

Mouth gags and packs. Several serious complications have arisen over the use of mouth gags which have been too hot. Judgments have been rendered where patients have suffered severe burns of the face. Check the temperature of the mouth gag before it is inserted into the mouth. Mouth packs for dental extractions, and tonsil and adenoid packs have led to several severe and fatal accidents, with judgments rendered against the physicians. Count the number of packs inserted, and count the number removed, and above all only use packs which have strings attached. Many a pack has slipped and produced obstructed breathing and death.

Spinal anaesthesia. Complications of spinal anaesthesia, such as paraplegia, broken needles, nerve root injuries, are familiar to all. It is sufficient to say here that we must use sterile equipment, with sterile technique; spinal drugs that have been autoclaved, not soaked; and *never* administer a spinal anaesthetic to an unwilling patient; to one who is suffering from low-back pain, or to one who has disease of the peripheral nervous system.

Intravenous anaesthesia. Barbiturates injected extra-vascularly have produced necrosis of tissue, and nerve damage, especially to the median nerve in antecubital fossa. Intra-arterial injections are not rare. Suffice it to say that we should use the weakest solution which will produce the desired result, and ensure that we are injecting into a vein by palpating the vessel for pulsation. Remember that a tourniquet will obliterate arterial pulsation, and that aberrant ulnar arteries are not rare.

Explosion. Explosion will be mentioned only briefly, but in Canada during the past year there have been two court actions over anaesthetic explosions. A judgment of several thousand dollars was rendered against an anaesthetist. Do you use the proper choice of anaesthetic agents in the presence of explosion hazards, and does your operating room meet the accepted Canadian hospital standards in the matter of explosion hazards?

Blood transfusions. Several suits based on deaths due to incompatible blood transfusions, and one based on a death due to air embolism during a pressure transfusion, have been tried recently in Canadian courts. There has been no effective defence.

Recent reports in the U.S.A. indicate that for every 3,000 blood transfusions, there occurs one death. We must ensure that we administer the proper type of blood to the patient; we must ensure that a proper cross-match has been done, and we must ensure that the blood designated for a certain patient is given to *that* patient. We must take extra precaution that so-called "unmatched" blood is really necessary.

Minimal analgesia. The technique of controlled apnoea with relaxant drugs plus minimal analgesia has been introduced in many centres. The advantage of this method of anaesthesia must be carefully weighed. In the United States, writs have been issued against anaesthetists employing this technique, in which patients have claimed, with proof that (*a*) they were "awake" during the operation, and heard the surgeons discussing the prognosis of their case, and (*b*) they experienced pain during the operative procedure. The judgment in these cases will be interesting.

Postoperative visits. Postoperative visits are most important. Some threatened actions, and some actual actions against anaesthetists would be avoided if we saw the patient postoperatively and had a friendly chat, and discussed their complaints.

Records. Accurate detailed records of the preoperative examination, the actual anaesthetic procedure, and postoperative visit must be kept. Hospital or physician's records are always demanded in a medico-legal case.

If a serious complication should occur, such as to the eye, the vocal chords, or the spinal nerve roots, always obtain the best consultant opinion available. The consultant should write his report on the hospital chart. An anaesthetist should never consider himself an authority in a medical field outside his own specialty.

Many physicians have needlessly involved themselves in legal complications by a careless "slip of the tongue" in the presence of a patient. An acknowledgment of a mistake or mention of a protective insurance plan can be fatal. However, notify your insurance company if you feel that dissatisfaction is evident and follow the advice offered by them. These protective insurance companies have excellent lawyers, trained in medico-legal matters.

The incidents above are just a few of the many pitfalls that anaesthetists encounter during their every-day practice. Whether we like it or not, we will be threatened or sued if we slip on some minor detail. The public is "suit" conscious, and we must protect ourselves and try to avert as many of these suits as possible.

I know this presentation may have sounded like a sermon. Sydney Smith, a London clergyman and wit of the nineteenth century, said: "Preaching has become a by-word for long and dull conversation of any kind; and whoever wished to imply, in any piece of writing, the absence of everything agreeable and inviting, calls it a sermon."

A medical-legal case is neither agreeable nor inviting, and I feel that we, as anaesthetists, could take better precautions; that we must realize that even the best of us have human frailties and that even the best of us may sometimes be careless. Remember, *"it could happen to you."*

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LES RESPONSABILITES MEDICO-LEGALES DE L'ANESTHESISTE

H. B. Graves, B.A., M.D., C.M.

L'ANNÉE 1942, dans les annales de l'anesthésie canadienne, demeurera une année dont se souviendront toujours les anesthésistes canadiens. C'est cette année-là que Griffith et Johnson ont publié leurs observations sur l'emploi du curare pour la première fois au cours de l'anesthésie générale. Plusieurs auteurs ont qualifié ce nouvel usage de curare: le plus grand progès en anesthésie durant les 25 dernieres années.

Combien parmi nous réalisent que, durant cette même année dans la province d'Ontario, il est survenu un autre évènement important qui devait avoir une portée transcendante sur la pratique de l'anesthésie au Canada? La cause de Hughston et Jost, cette année-là, devenait la premiére cause, dans toutes les cours de justice du Canada, où un anesthésiste était poursuivi seul pour une prétendue négligence. Du point de vue légal, l'anethésie devenait majeure.

Avant 1942, on reconnaissait le haut commandement du chirurgien dans la salle d'operation, aussi bien sur l'anesthésie que sur l'anesthésiste. On tenait le chirurgien responsable de tous les méfaits de l'anesthésique, bien que le médecin qui administrait cet anesthésique pouvait être tenu conjointement responsable.

Dans la cause de Hughston et Jost à laquelle nous faisons allusion plus haut, l'anesthésiste seul était poursuivi pour prétendus méfaits à la suite de l'administration intra-veineuse de Pentothal. Le chirurgien a comparu comme témoin, mais n'a pas été impliqué dans l'action. L'anesthésie était devenue une spécialité et l'anesthésiste un spécialiste.

Au cours des dernières années en Grande-Bretagne, aux Etats-Unis, au Canada, les anesthésistes ont eu à répondre à des menaces, des sommations, des actions, des jugements et à faire des ententes.

Le but de ce travail est d'attirer l'attention sur des faits qui peuvent aider à prévenir ces menaces, sommations ou actions.

Rappelons-nous que, en qualité d'anesthésistes, nous sommes médecins, et que tout médecin peut être poursuivi. Personne peut empêcher un malade de prendre action contre vous, que cette action soit justifiée ou non.

Quelles sont les précautions qu'il nous faut prendre? J'en enumérerai seulement quelques-unes.

Le contact personnel avec le malade: L'histoire et l'examen physique

L'anesthésiste en acceptant d'administrer l'anethésie, prend une assez lourde responsabilité. L'anesthésie moderne conduit de nombreux malades bien près de la mort. En conséquence, il devient essentiel que l'anesthésiste soit renseigné sur l'histoire médicale du malade et encore plus particulièrement sur l'état physique de ce malade.

Cela suppose un contact personnel entre l'anesthésiste et le malade. Le contact personnel va inspirer confiance au malade, puis un malade qui a confiance à un médecin, vraisemblablement, sera moins enclin à déposer une plainte contre ce médecin.

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Plusieurs malades ont refusé de payer leurs comptes sous l'un des prétextes suivants: (*a*) ils n'avaient pas rencontré cet individu fantôme, l'anesthésiste; (*b*) ils n'avaient pas fait d'entente avec cet individu nébuleux pour l'administration de l'anesthésie.

Chacun de nous réalise que, pour faire un choix judicieux des agents anesthésiques aussi bien que des techniques d'anesthésie, il est essentiel de savoir si le malade est allergique à certains médicaments, s'il a souffert antérieurement de cephalée post-rachidienne, de douleurs dans le dos, s'il a déjà vécu des aventures malheureuses avec l'anesthésie, etc.; puis, nous savons tous que certains états pathologiques spécifiques deviennent une contridication à certains médicaments et à certaines techniques.

En qualité d'anesthésistes actifs, nous devrions visiter personnellement le malade, recueillir les renseignements ci-haut mentionnés et, ce qui est encore plus important, nous devrions inscrire sur le dossier de l'hôpital, avant l'administration de de l'anesthésie, l'histoire du cas et l'examen physique appropriés. De nombreuses sommations ont été émises pour de prétendus dommages aux dents—en quel état étaient ces dents avant l'administration de l'anesthésie? Récemment, nos associés dans la pratique de la spécialité ont reçu une sommation pour une voix demeurée rauque à la suite d'une intubation. La poursuite a été abandonnée quand il est devenu possible de prouver que la malade avait déjà eu la voix rauque bien avant d'être soumise à l'anesthésie.

Voilà quelques exemples illustrant bien toute l'importance qu'il y a de "connaître son malade" avant de le soumettre à une anesthésie.

Obtenir le consentement pour l'anesthésie et la chirurgie

Avant de commencer un anesthésie, on devrait toujours avoir obtenu le consentement écrit du malade à un moment où il était dans un état d'esprit normal, consentement pour l'anesthésie et pour la chirurgie. Autrement, l'anesthésiste pourrait être tenu responsable d'assaut. Il est bien essentiel d'obtenir ce consentement alors que le malade est dans un état d'esprit normal; un consentement signé après la prémédication ne devrait pas être accepté; en effet, la prémédication peut produire de l'amnésie. Si le malade est mineur, il s'impose d'obtenir la signature d'un parent ou d'un tuteur.

Dans notre hôpital, il y a une entente: on ne commence pas une anesthésie si la formule de consentement n'est pas signée.

Si le malade est dans un état tel qu'il ne peut pas signer, nous insistons pour obtenir le consentement écrit d'un proche parent ou nous demandons au chirurgien de signer une attestation de la nécessité absolue de l'opération, en ce qui concerne les membres du personnel ou les indigents, nous demandons la signature d'un administrateur de l'hôpital. Chacun a lu dans les journaux, à plusieurs reprises, que des malades ont poursuivi des médecins pour les avoir soumis à une anesthésie ou avoir pratiqué une opération sans leur consentemant préalable.

Identification du malade

Chacun a entendu raconter qu'un faux malade avait été opéré, que la jambe en santé avait été coupée, que le bon œil avait été enlevé. Ici au Canada, il y a eu des jugements de rendus contre les médecins pour des milliers de dollars pour des cas semblables de négligence. Il appartient à l'anesthésiste autant qu'au chirurgien de vérifier que c'est le bon malade qui doit être opéré et que c'est la bonne partie du corps qui doit subir cette opération. Vérifiez le dossier et assurez-vous que c'est le bon malade. Il est arrivé que des malades du même nom, venant de la même salle, soient amenés à la salle d'opération pour des opérations bien différentes.

Faites identifier le malade par le chirurgien et en aucune circonstance ne commencez une anesthésie avant l'arrivée du chirurgien. Je me souviens d'un incident ou une anesthésie durait déjà depuis une heure, lorsque l'on a appris que le chirurgien était en train d'opérer dans un autre hôpital. Quelle sorte de justification un anesthésiste aurait-il pu faire valoir s'il était arrivé un accident au cours de cette anesthésie?

Administration de l'anesthésie

Il faut prendre des mesures de sécurité pour administrer l'anesthésie à des malades qui ont l'estomac plein. On pourrait dire plus explicitement qu'on ne devrait jamais adminstrer une anesthésie à de semblables malades. Il existe des statistiques permettant d'établir que le plus grand nombre de morts sous anesthésie étaient dues à l'aspiration du contenu gastrique. Dans une grande ville, à la suite d'une querelle de rue, on amène à l'hôpital un homme souffrant d'une fracture du maxillaire. On savait que ce malade avait mais fut cédulée comme telle. On a commencé l'anesthésie, le malade s'est régurgité dans les bronches et est mort. L'assaillant a été accusé, non pas d'assaut mais d'homicide involontaire et un mandat a été émis egalement contre l'anesthésiste pour participation à cet homicide involontaire.

Il est difficile d'obtenir que tous les estomacs soient vides, particulièrement dans les cas de maternité. Mais il est possible de retarder la plupart des opérations de 4 à 5 heures ou encore de vider un estomac ou d'installer un tube gastrique.

Notre outillage doit être en bon état de servir et principalement la machine à anesthésie. On a constaté des brûlures de la face par la chaux sodée avec la technique du "va et vient" à cause d'un contenant défectueux; de nombreux cas d'œdème pulmonaire sont survenus à cause de valves à éther inversées; plusieurs morts ont été attribuées à des erreurs de cylindres aux différents débitmètres de la machine. Vos machines à anesthésie ont-elles système de sécurité? Employez-vous les légendes de couleurs reconnues pour les cylindres des gaz anesthésiques?

Les seryngues, les cabarets à rachianesthésie, à anesthésie régionale devraient tous être stérilisés à l'autoclave. Les ampoules, principalement celles qui contiennent des solutions pour anesthésie locale, ne devraient jamais baigner dans une solution contenant de l'alcool ou de la formaline ou une solution antiseptique quelconque. Chacun est au courant du fameux procès vécu en Angleterre il y a trois ans, au sujet de la rachianesthésie où le jugement laissait entendre qu'à partir de ce moment l'emploi d'ampoules stérilisées dans des solutions serait l'équivalent d'une négligence. Assurez-vous, de plus, que le médicament que vous employez est fabriqué par une mainson de bonne réputation.

Placez sur le bras du malade un appareil à tension artérielle; notez avant et pendant l'anesthésie la tension artérielle et le pouls. Un jour,, il survient une mort dans une salle d'opération; l'appareil à tension de l'anesthésiste étant brisé, la tension n'était pas inscrite au dossier. La compagnie d'assurance protégeant l'anesthésiste a payé la casse sans essayer de contester l'action.

Avant de commencer une anesthésie générale, fixez le malade sur la table. Plusieurs hôpitaux ont été poursuivis conjointement avec le personnel à cause de fractures survenues à l'occasion d'une chute de la table d'opération. Assurez-vous qu'un infirmier ou une infirmière soit là surtout si la malade est une femme, ayez une infirmière comme témoin sans qu'il ne soit nécessaire de détailler les raisons.

Surveillez l'installation des malades

Les pressions exercées sur des nerfs vulnérables tels le cubital, le poplité, le plexus brachial, etc., peuvent produire et, de fait, ont produit des séquelles neurologiques qui ont valu des poursuites légales. Pour plus de sécurité: faites installer le malade par le personnel de l'hôpital et ainsi vous ne pourrez pas être tenus responsables des complications éventuelles.

On a dû pratiquer des amputations de bras et de jambes à la suite de tourniquets mal installés. Si l'anesthésiste aide à installer un tourniquet, il doit également, en conséquence, accepter la responsabilité d'enlever le tourniquet quand l'opération est terminée.

Les contretemps de l'anesthésie

Ces contretemps de l'anesthésie sont responsables du plus grand nombre de menaces, sommations et jugements. Le temps ne me permettra pas de les passer tous en revue, mais je voudrais en mentionner quelques-uns.

Aire orbiculaire. Les ulcérations de la cornée dues à un agent anesthésique volatile ou à un traumatisme au cours ou à la suite d'une anesthésie ont entraîné un bon nombre d'ennuis sérieux.

On a observé de la conjonctivite et même de la cécité à la suite de pression prolongée sur l'œil; on a également noté des névrites supra-orbitaires à la suite de pression. Prenez-vous toutes les mesures de sécurité désirables pour protéger la région orbitaire?

Les dents. Les dents brisées, les ponts brisés, l'extraction dentaire à la suite de traumatisme, particulièrement chez les enfants, ont accumulé le plus grand nombre de menaces. Au cours de l'intubation, protégez-vous adéquatement les dents? Si vous brisez des dents et que vous ne trouvez pas les morceaux, prenez-vous soin de radiographier le thorax pour les localiser? Le bris de dents au cours d'une anesthésie constitue un risque accepté aujourd'hui, mais il ne faut jamais accepter toute la responsabilité financière de la réparation.

Ouvre-bouche et tampons. On a rapporté plusieurs complications sérieuses à la suite de l'emploi d'un ouvre-bouche trop chaud. Il y a des jugements de rendus à la suite de brûlures de la face dans de telles circonstances.

Vérifiez la température de l'ouvre-bouche avant de l'installer dans la bouche. Les tampons dans le pharynx au cours des extractions dentaires, les tampons hémostatiques employés au cours des amygdalectomies et des curettages d'adénoïdes ont été responsables d'accidents graves et de fatalités suivis de jugements contre les médecins. Il s'impose de compter les tampons utilisés, d'en faire le décompte après l'intervention et de n'utiliser, si possible, que des tampons porteurs d'un long pendatif. Plus d'un tampon est disparu, est allé obstruer les voies respiratoires et a causé la mort.

La rachianesthésie. Les complications de la rachianesthésie telle la paraplégie, une aiguille brisée, une racine nerveuse traumatisée ne font plus de doute pour personne. Qu'il nous suffise de mentionner ici qu'il faut employer un outillage stérile et une technique bien aseptique, les médicaments utilisés à cet effet doivent passer à l'autoclave et non pas séjourner dans des solutions; surtout, il ne faut jamais faire une rachianesthésie à un malade qui n'en veut pas; il en est ainsi pour celui qui souffre de douleurs lombaires ou de maladies nerveuses périphériques.

L'anesthésie par voie endoveineuse. L'injection de barbituriques dans les vaissaux a entraîné occasionnellement des nécroses tissulaires et des séquelles neurologiques, particulièrement au median dans la fosse antécubitale. Les injections dans une artère sont encore assez fréquentes. Qu'il nous suffise de conseiller ici l'emploi de la solution la plus diluée qui soit suffisante pour obtenir les effets désirés et de s'assurer que l'injection se fait dans une veine en recherchant une pulsation sur le vaisseau. A retenir qu'un tourniquet peut arrêter la circulation artérielle et que les artères cubitales aberrantes ne sont pas rares.

Les explosions. Je ne ferai qu'une brève allusion aux explosions, mais, toutefois, l'année dernière, au Canada, il y a eu deux actions de prises à cause d'explosions. Un jugement de plusieurs milliers de dollars a été rendu contre un anesthésiste. Quand il y a risque d'explosion, faites-vous attention au choix de l'agent? Vos salles d'opération remplissent-elles les exigences requises dans les standards des hôpitaux canadiens en ce qui concerne les explosions?

Transfusions sanguines. De nombreuses poursuites consécutives à des morts survenues à la suite de la transfusion d'un sang incompatible et une poursuite à la suite d'une mort par embolie gazeuse au cours d'une transfusion sous pression sont passées en cour récemment au Canada. On n'a pas présenté de défense efficace. On rapporte que, aux Etats-Unis, il survient une mort par 3000 transfusions, il faut être positif que le malade reçoit du sang d'un groupe qui lui convient: que le groupe a été vérifié, de même que l'agglutination et que le sang destiné à un malade va être donné à ce malade. En ce qui concerne le sang universel où l'épreuve d'agglutination n'a pas été faite, il ne devrait être donné qu'en absolue nécessité.

L'analgésie minimal. Dans plusieurs centres, on a commencé à employer la technique de l'apnée controlée en se servant de substances curarisantes et en donnant un minimum d'analgésie. Il faut bien peser les avantages de cette méthode. Aux Etats-Unis, il y a eu des sommations d'adressées à des anesthésistes qui avaient employé ces méthods, car les malades ont prétendu, preuves à l'appui: (*a*) qu'ils étaient éveillés durant l'opération et qu'ils ont entendu les chirurgiens discuter le pronastic de leur cas; et (*b*) qu'il ont ressenti de la douleur durant l'opération. Les jugements dans ces cas ne manqueront pas d'intérêt.

Les visites post-opératoires. Les visites post-opératoires sont de toute importance. Il y a un grand nombre de recours en justice qui seraient évités si nous voyions nos malades au cours des suites opératoires et discutions amicalement avec eux de leurs griefs.

Les dossiers. Il faut absolument conserver dans les dossiers les détails précis de l'examen pré-opératoire, de l'anesthésie et des visites subséquentes. Dans les causes médico-légales, les dossiers de l'hôpital et du médecin sont toujours requis.

S'il survient une complication sérieuse, soit à un œil, aux cordes vocales, ou à des racines nerveuses, il faut toujours recourir à l'opinion du meilleur consultant possible. Le consultant devrait écrire son rapport sur le dossier de l'hôpital. Un anesthésiste ne devrait jamais se considérer comme une autorité dans une spécialité médicale autre que la sienne.

Il y a plusieurs médecins qui ont été entraînés inutilement dans des complications légales à cause d'une indiscrétion imprudente en présence d'un malade. La reconnaissance d'une erreur ou l'aveu que vous avez une assurance qui vous protège peut vous être fatal. Toutefois, avertissez votre compagnie d'assurance si vous avez l'intuition qu'il y a du mécontentement et suivez la ligne de conduite qu'elle vous tracera. Les compagnies d'assurance emploient d'excellents avocats versés dans les conflits médico-légaux.

Les incidents ci-haut mentionnés ne sont qu'un petit nombre des mauvais pas que les anesthésistes peuvent faire au cours de leur pratique quotidienne. Qu'on le veuille ou non, nous sommes exposés à la poursuite pour l'omission des plus petits détails. Le public a une tendance a recourir à la justice. Il nous faut nous protéger et faire échouer le plus grand nombre possible de ces poursuites.

J'ai l'impression que ce travail a pu avoir l'apparence d'un sermon. Sydney Smith, un ministre de Londres, à l'esprit du dix-neuvième siècle, disait: "La prédication est devenue un mot de passe pour n'importe quelle conversation longue et ennuyeuse; et celui qui veut laisser entendre, dans un article, qu'il n'y aura rien d'agréable ou d'attrayant, l'appelle un sermon."

Une cause médico-légale n'a rien d'agréable ou d'attrayant et j'ai l'impression que nous, anesthésistes, devrions faire plus attention; il nous faut réaliser que même le meilleur d'entre nous à des points faibles et que le plus fin peut avoir des distractions.

Le mot d'ordre: *"Cela peut vous arriver."*

NEWS LETTER

The Annual Meeting

The registration at the Annual Meeting of the Society at the Bessborough Hotel in Saskatoon was somewhat smaller than usual, but the calibre of the programme and the superb social arrangements made this Meeting one of the outstanding events in the history of the Society. We are certain that all who attended are pleased to have been there, and those who did not or could not undoubtedly will have ample time for regret.

Upper left: Dr. E. A. Gain, Vice-President, presents an inscribed gavel to Dr. M. W. Bowering, retiring President.

Upper right: Professor R. N. H. Haslam, Department of Physics, University of Saskatchewan, guest speaker at the dinner.

Below, left to right: Dean Wendel McLeod, Dean Emeritus, W. S. Lindsay, and Dr. Gordon Wyant of the College of Medicine, University of Saskatchewan.

Above: Miss E. R. Campbell, Assistant Secretary, and Mrs. J. E. Marshall, Hamilton, Ontario.

Below: At the Head Table: Dr. James Forrester, Mrs. R. A. Gordon, and Dr. Alan B. Noble, Past-President.

We are still wondering how the Anaesthetists managed to win the ball game from the Exhibitors at the Saskatoon Meeting. Surely this is carrying salesmanship a little far. Perhaps the commercial boys may do better at golf or water polo at the Seigniory Club next year.

The President, Dr. M. W. Bowering, and the Secretary, Dr. R. A. Gordon, were interviewed on an afternoon television show during the Saskatoon Meeting. They are still suffering insomnia as they try to answer the question "What is an anaesthetic?" The panel of experts assembled for the closing hour of the Meeting was no help whatever in providing an answer.

The President, Dr. M. W. Bowering, presents a bouquet of yellow roses to Miss E. R. ("Happy") Campbell, Assistant Secretary.

We were interested at Saskatoon to hear identical comment from a seven-year-old "dependent," a "visiting lady," and a middle-aged anaesthetist. With some small variations, they all said: "Gosh! I didn't know the West was like this!"

Now is the time to make sure that you get to the 1958 Meeting at the Seigniory Club in Quebec, the dates June 23, 24 and 25—and if the Council can arrange it, the 26th. Moreover, if you want a chance to talk at that Meeting, now is the time to let the Secretary know about it.

Back issues of the Journal are urgently required to complete the volumes in a number of libraries. Please consult the list on the last page of this issue.

DR. HAROLD GRIFFITH RETIRES

ON MONDAY, June 3, 1957, Anaesthesia Night in Montreal, some two hundred Montreal anaesthetists and their spouses gathered at a banquet to honour Professor Harold R. Griffith on the occasion of his retirement from the post of Professor of Anaesthesia and Chairman of the Department at McGill University, and his promotion to the post of Professor Emeritus.

Dr. Alan B. Noble, who acted as chairman of the evening, graciously thanked Professor Griffith on behalf of the many present who are still his students, despite their graying hair, for his efforts towards the advancement of anaesthesia in Montreal. Dr. Georges Cousineau, in proposing the health of Mrs. Griffith and the ladies, recalled a friendship of twenty years with the Griffith family.

Following the presentation, by Dr. Robert Ferguson, of an oil painting of the Medical Building, Dr. Griffith thanked the assembled company, recalling some of his early experiences as an anaesthetist, urging continued co-operation among the anaesthetists in Montreal and the Province of Quebec, and stating that the recent establishment of a full-time department of Anaesthesia Research at the University was "a dream come true."

Other speakers who paid tribute to Dr. Griffith were Professor Wesley Bourne, and Professor C. P. Martin, representing Dean Lloyd Stevenson.

Dr. R. G. B. Gilbert has been appointed Professor and Chairman of the Department of Anaesthesia at McGill University.

Dr. R. A. Gordon has been promoted to the rank of Assistant Professor and Dr. R. H. Meredith to the rank of Associate in the Department of Anaesthesia at the University of Toronto.

LIFE MEMBERS

Dr. Wesley Bourne, Dr. Harry J. Shields and Dr. Beverley C. Leech were elected Life Members of the Canadian Anaesthetists' Society at the Annual General Meeting on June 25 at Saskatoon.

NEWFOUNDLAND DIVISION

The Newfoundland Division of the Canadian Anaesthetists' Society continues to be active. Now there are eleven members, at least there will be when all these who plan to join do so.

In the past year, largely through the efforts of the division, the anaesthetic equipment in the St. John's hospitals has markedly improved and compares to what is seen in larger centres. There is an organized anaesthetic department at the General Hospital, St. John's, with a recognized programme for one year residency training. Two of the other hospitals in St. John's recently organized staffs. Attempts to have departments of anaesthesia have not been successful as yet, although some progress has been made in this direction. It is hoped that they will be established soon and efforts are continuing towards realization of this objective.

Dr. W. P. Jones of the resident staff of the General Hospital is joining the Cleveland Clinic, Cleveland, Ohio, for further anaesthetic training.

Dr. John W. K. Tyl of the resident staff of the General Hospital is going to continue his anaesthesia training in Montreal in the autumn.

Clinical programmes have been better worked out and organized and plans are being made to improve these further.

SASKATCHEWAN DIVISION

Dr. & Mrs. G. M. Wyant are to be congratulated on the birth of their fourth son Gordon Spencer, on July 9.

Dr. Thomas A. Christie has returned to Regina from the University Hospital, Saskatoon, and is in practice there with the Associated Anaesthetists.

Dr. Geordis M. Aasheim is continuing her training at King County Hospital, Seattle.

Dr. Hannaliese Kralemann is continuing her training at the University of Minnesota Hospital.

Dr. Frank C. Haley of Calgary and the University of Alberta has joined the Department of Anaesthesia, University Hospital, at Saskatoon as Assistant Resident.

Dr. Otto W. Schuh completed his first year of training at the Regina General Hospital and has now joined the Department of Anaesthesia, University Hospital, at Saskatoon, as Assistant Resident.

Dr. Edward T. Thomas, F.F.A.R.C.S., of England, has joined the Department of Anaesthesia, University Hospital, Saskatoon, as Teaching and Research Fellow.

It is rumoured that Dr. E. Asquith and Dr. C. J. Kilduff gave the Regina Siamese twins their first anaesthetic.

ANNOUNCEMENT

The scientific papers and addresses of Dr. Ralph Waters have been published in a single volume of 130 pages under the sponsorship of Dr. Robert A. Hingson of the Department of Anesthesia, Western Reserve University, School of Medicine, Cleveland, Ohio, U.S.A. A limited number of copies of this volume are available to anaesthesiologists throughout the world at a cost of $4.00 per copy.

OBITUARY

DOCTOR WALTER LAWSON MUIR

The death of Dr. Walter Muir of Halifax occurred on May 26, 1957, in his seventy-sixth year.

Dr. Muir was one of the pioneer anaesthetists in the Atlantic Provinces, and was head of the Departments of Anaesthesia of the Victoria General Hospital in Halifax and of the Faculty of Medicine of Dalhousie University from 1927 to 1946. He was a Senior Member of the Canadian Medical Association and a Life Member of the Canadian Anaesthetists' Society.

Dr. Muir was born at Truro, Nova Scotia, in 1880. He graduated from King's College at Windsor in 1903 with a Bachelor of Arts degree and received his medical qualification from McGill University in 1907. Following post-graduate study in Montreal he established a practice in Truro in 1910, but left in 1914 to serve as a Battalion Medical Officer with the Canadian Expeditionary Force. On his return from overseas he was appointed to the Departments of Anaesthesia of Camp Hill Military Hospital and the Victoria General Hospital in Halifax.

Dr. Muir enjoyed a wide circle of friendship and held the respect, admiration and affection of his colleagues in the medical profession and particularly in his chosen speciality of anaesthesia.

BOOK REVIEWS

RECENT ADVANCES IN ANAESTHESIA AND ANALGESIA. By. C. LANGTON HEWER and J. ALFRED LEE. Eighth edition. London: J. & A. Churchill Ltd.; Toronto: British Book Service. 1957. $6.80.

Hewer's *Recent Advances* has long been one of the standard textbooks in anaesthesia in the English-speaking world. Previous editions have had a reputation as a primary textbook. The present edition no longer deals with elementary procedures and principles, but concentrates on important aspects of recent changes in concepts and techniques in the field of anaesthesia. This work represents a monumental effort in examining the recent literature, and the authors are to be congratulated on their success in presenting a vast amount of information in a relatively small volume. This book is most highly recommended for all who are interested in keeping abreast of current developments in anaesthesia.

R.A.G.

MORPHINE AND ALLIED DRUGS. By A. K. REYNOLDS and L. O. RANDALL. Toronto: University of Toronto Press. 1957. $10.00.

The authors have gathered material from a vast number of sources to present to clinician and laboratory investigator the reliable information about morphine and allied drugs. This is no biased account, for the reports of clinic and laboratory are often conflicting, and the wide species variation to these compounds is particularly noticeable as their effects on humans, dogs, cats, guinea pigs and many other animals are mentioned.

There are comparisons between morphine and other drugs with particular reference to tolerance, addiction and analgesic potency.

The chapters on morphine, meperidine, alphaprodine, the morphinan series, and the antagonists to analgesics are of interest to anaesthetists. The references to chemical structure are conveniently illustrated, and, with the orderly presentation of the various drugs, aid in the understanding of the theory of action of the compounds proposed at the end.

There is no doubt that there is still much to be discovered in this field and that the present antagonists leave much to be desired.

S.A.F.

MUSCLE RELAXANTS IN ANESTHESIOLOGY. By FRANCIS F. FOLDES. Toronto: Ryerson Press. $6.00.

Dr. Foldes has written a book which will surely become most popular with the practising anaesthetist and with the examination candidate.

Primarily a review of the practical and theoretical aspects of the problems related to the muscle relaxants, this book also gives a working account of modern balanced anaesthesia.

References are given in such number that an index of authors' names is included, making the bibliography all the more useful.

Dr. Foldes champions assisted respiration and suggests that the commonly used technique of controlled respiration is the source of many of the problems arising in cases in which relaxants have been used. He selects a suxamethonium drip as the method of choice in a wide range of instances but, in addition, describes techniques utilizing other agents. It is interesting to note that somewhat low total gas flows are recommended and that the routine use of atropine prior to edrephonium is suggested.

This book may be strongly recommended as an easily readable, reliable survey of the subject.

H.B.F.

CANADIAN ANAESTHETISTS' SOCIETY, NEW MEMBERS

THE FOLLOWING NEW MEMBERS were approved by the Annual General Meeting of the Society at Saskatoon, Saskatchewan, on June 25, 1957.

British Columbia

Dr. William Anthony Doll (M.E.)	Vancouver General Hospital
Dr. Joseph Mitchell Hiddleston (M.E.)	Vancouver General Hospital
Dr. Edward Noel Hughes (M.E.)	2995 W. 34th Ave., Vancouver
Dr. Irene Edith Millar (M.E.)	Vancouver General Hospital
Dr. Tom Everard Powell (M.E.)	Vancouver General Hospital
Dr. John Raymond Stone (O.M.)	3656 Crestview Rd., Victoria
Dr. Donald Andrew Walker (M.E.)	4112 Price Crescent, S. Burnaby
Dr. Floyd George Williams (M.E.)	3465 W. 23rd Ave., Vancouver
Dr. George Harold Laycraft (M.E.)	Vancouver General Hospital
Dr. Alun Philip Thomas (O.M.)	Irving Clinic, P.O. Box 150, Kamloops
Dr. Alexander Duncan McDougall (O.M.)	Irving Clinic, P.O. Box 150, Kamloops
Dr. Guy Screech (M.E.)	3680 Cadboro Bay Rd., Victoria

Alberta

Dr. Alfred Kenneth Bradshaw (M.E.)	8621–108A St., Edmonton
Dr. Edgar G. Diamond (M.E.)	828-20th Ave. N.W., Calgary
Dr. Carl H. Heuchert (O.M.)	223 Medical Arts Bldg., Calgary
Dr. Ebba Kirkebeck (O.M.)	509-15th Ave. N.E., Calgary
Dr. John Dalton Manes (O.M.)	300 Medical Arts Bldg., Calgary
Dr. Adraan W. J. Starnick (O.M.)	Medical Arts Bldg., Calgary
Dr. John Bertram Collip (M.E.)	11141–91st Ave., Edmonton
Dr. Robert Irvine McCalla (O.M.)	9566–83rd St., Edmonton
Dr. Solly Gerard Paletz (Cert)	11444–71st Ave., Edmonton

Saskatchewan

Dr. Geordis M. Aasheim (M.E.)	University Hospital, Saskatoon
Dr. Chung Ai Chang (M.E.)	1227–15th St., Saskatoon
Dr. Thomas A. Christie (M.E.)	P.O. Box 34, 1004 McCallum Hill Bldg., Regina
Dr. Hannaliese Kralemann (M.E.)	University Hospital, Saskatoon
Dr. Kwang-Yi Lee (M.E.)	University Hospital, Saskatoon

Manitoba

Dr. Francis Renkin Cullen (M.E.)	50 Ruby St., Winnipeg
Dr. John Culligan (M.E.)	Dept. of Anaesthesia, Winnipeg General Hospital, Winnipeg
Dr. Thorberg Johannesson (M.E.)	613 Alverstone St., Winnipeg
Dr. Thomas N. F. Todd (O.M.)	620 Lindsay St., Winnipeg
Dr. Dorothy Barnhouse (Cert) re-instated	283 Belvedere St., St. James, Winnipeg 12

Ontario

Dr. Daniel Antonevych (M.E.)	16 Briarcroft Rd., Swansea, Toronto
Dr. Matthew Bazian (O.M.)	159 Stinson, Hamilton
Dr. Jeremiah Dillon (M.E.)	133 Belsize Dr., Toronto
Dr. Donald Harold Dunn (O.M.)	1189 Queen Victoria Ave., Lorne Park
Dr. Anthony Gagliano (M.E.)	St. Joseph's Hospital, Toronto
Dr. C. W. P. Lunderville (O.M.)	48 Broadpath, Don Mills, Toronto
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Dr. R. L. Matthews (M.E.)	Forest

Dr. Rudolph Frank Ohlke (Cert)	2076 Harvest Dr., Port Credit
Dr. Edward Petrovich (M.E.)	2686 Bloor St. W., Apt. B31, Toronto
Dr. G. Owen Warr (O.M.)	138 Kerr St. N., Oakville
Dr. Francis A. Duggan (M.E.)	Sunnybrook Hospital, Toronto
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Dr. Manie Rotenberg (O.M.)	26 Farrington Dr., Willowdale

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Dr. Beryl Jones (M.E.)	Royal Victoria Hospital, Montreal
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Dr. Gerard Lavoie (M.E.)	5532 rue Lacovdaire, Montreal
Dr. Pierre Paquet (M.E.)	259 D'Aiguillon, Quebec
Dr. Paul Quan (M.E.)	Montreal Children's Hospital, Montreal
Dr. Jean Quintal (M.E.)	6905–21st Ave., Rosemont, Montreal
Dr. Helmut August Richter (M.E.)	Arvida
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Dr. Ian Harper (M.E.)	Montreal General Hospital, Montreal
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Nova Scotia

Dr. Gordon Lloyd Goulding (M.E.)	105 London St., Halifax

New Brunswick

Dr. S. T. Love (O.M.)	361 Regent St., Fredericton
Dr. Matthew H. Swan (O.M.)	78 Rosebery St., Campbellton

Prince Edward Island

Dr. Gilbert J. Gallant (O.M.)	281 Schurman Ave., Summerside

Newfoundland

Dr. William P. G. Jones (M.E.)	General Hospital, St. John's
Dr. J. W. K. Tyle (M.E.)	31 Topsail Rd., St. John's
Dr. John James Kennedy (Cert)	188 LeMarchant Rd., St. John's

Other Countries

Dr. William Meredith Jones (M.E.)	886 Louise Circle, Apt. F., Durham, N.C.
Dr. Joseph McCammon (M.E.)	212–20th Ave. S.W., Rochester, Minn.
Dr. William Norman Rallason (F.F.A.R.C.S., Eng.)	83 Newland Park, Hull, England

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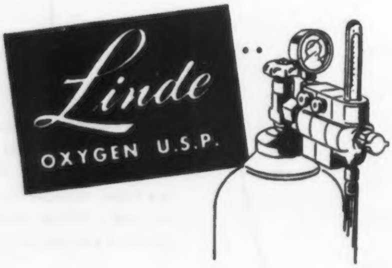

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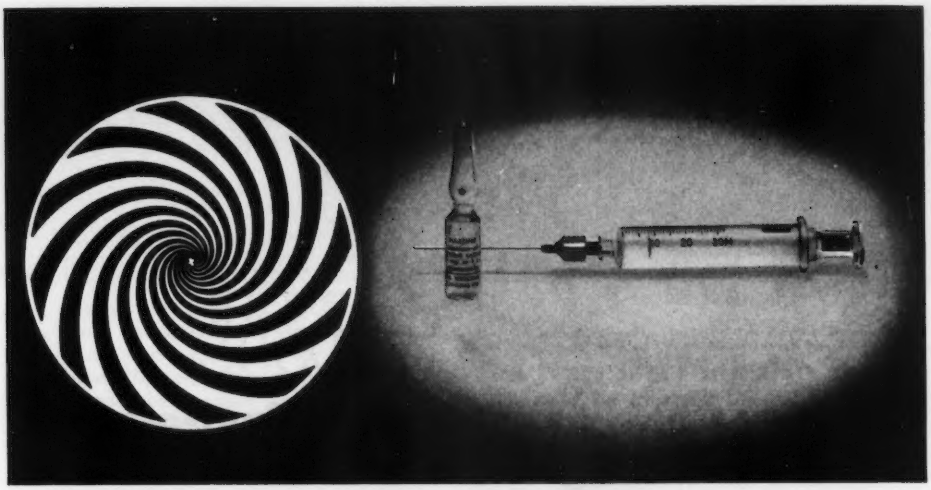

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1. Dent, S. J., Ramachandra, V., and Stephen, C. R.: Postoperative Vomiting: Incidence, Analysis and Therapeutic Measures in 3000 Patients, Anesthesiology. To be published. 2. Marcus, P. S., and Sheehan, J. C.: The Treatment of Postoperative Vomiting, Anesthesiology, *16*:423, 1955.

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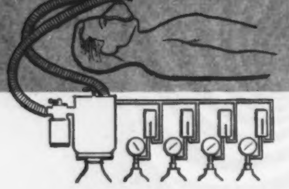

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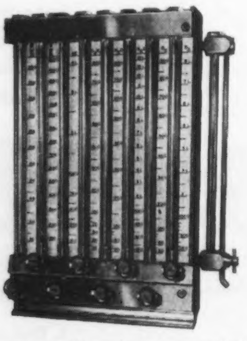

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". . . it is thought that the advantages offered by the use of this tube, both as to the convenience to the surgeon and to the safety of the patient, warrant its further use." REF.: Siebecker, K. L., Land, J. F.—*Anesthesiology* —17:660; 1956.

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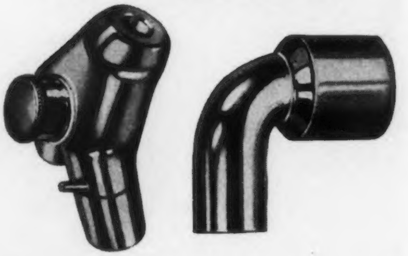

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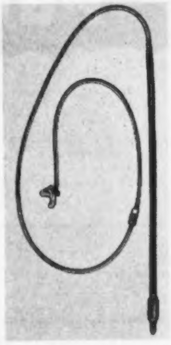

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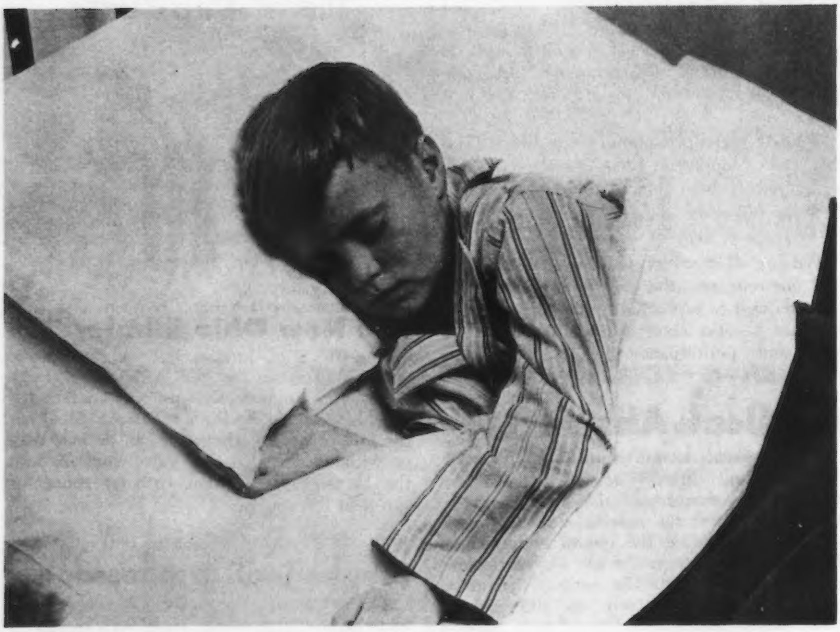

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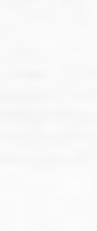

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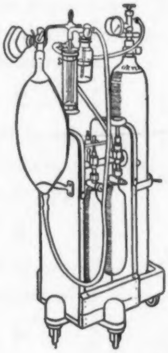

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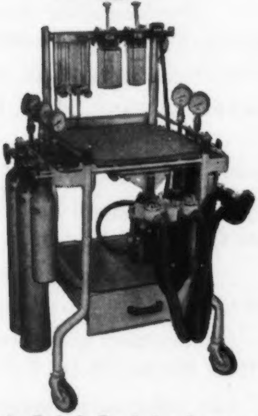

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1. Webster, C.W., C.M.A.J. Oct. 1953.

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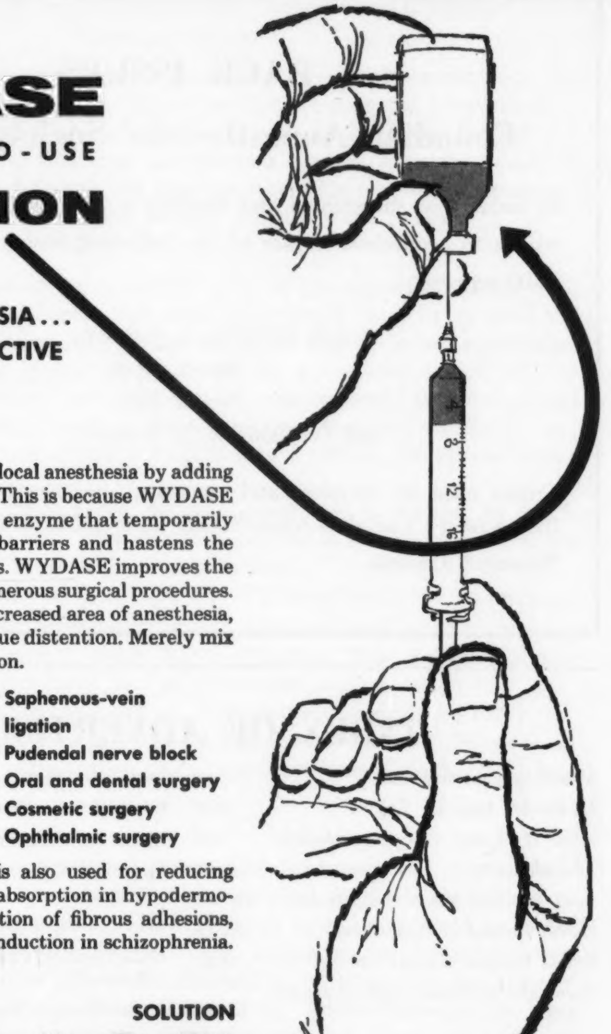

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